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=> s l1 and KDR
L2          145 L1 AND KDR

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L3           16 L2 AND ACTIVATION

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L4             8 DUP REMOVE L3 (8 DUPLICATES REMOVED)

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L4   ANSWER 1 OF 8  CAPLUS  COPYRIGHT 2006 ACS on STN
2006:765251   Document No. 145:211037  Preparation of pyrazolyl aryl ureas as
     modulators of the protein kinase activation state for treatment
     of inflammation and hyperproliferative diseases.  Flynn, Daniel L.;
     Petillo, Peter A. (Deciphera Pharmaceuticals, LLC, USA).  PCT Int. Appl.
     WO 2006081034 A2 20060803, 305pp.  DESIGNATED STATES: W:  AE, AG, AL, AM,
     AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE,
     DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN,
     IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA,
     MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO,
     RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US,
     UZ, VC, VN, YU, ZA; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK,
     ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN,
     TD, TG, TR.  (English).  CODEN: PIXXD2.  APPLICATION: WO 2005-US47597
     20051223.  PRIORITY: US 2004-638987P 20041223.
GI
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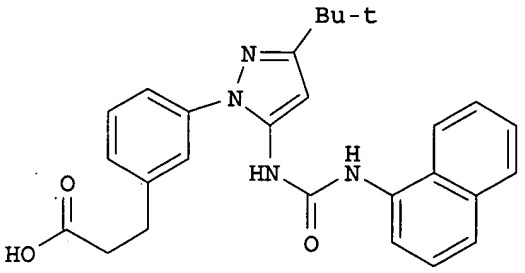

II

AB Novel compds. and methods of using those compds. for the treatment of inflammatory conditions, hyperproliferative diseases, cancer, and diseases characterized by hypervascularization are provided. In a preferred embodiment, the compds. of the invention modulate the activation state of p38 kinase protein, abl kinase protein, bcr-abl kinase protein, braf kinase protein, VEGFR kinase protein, or PDGFR kinase protein. The compds. of the invention I have general formula (R1-(X)j)m-A-NH-L-NH-D-(E)q-(Y)t-Q wherein R1 = aryl, heteroaryl, and heterocyclyl; X and Y = individually O, S, alkynyl, alkenyl, etc.; A = an aromatic, monocycloheterocyclic, or bicycloheterocyclic ring; D = Ph or a 5-6-membered heterocyclic ring; E = Ph, pyridinyl, or pyrimidinyl; L = -C(O)- or -S(O)2-; j,m,q,t = 0-1; and Q = a substituted ring or ring system. Over 500 compds. were prepared For example, hydrogenation of 3-(3-aminophenyl)acrylic acid Me ester provided the propionate, which was subsequently converted to the hydrazine. Reaction of the hydrazine with 4,4-dimethyl-3-oxopentanenitrile afforded Me 3-[3-(3-tert-butyl-5-amino-1H-pyrazole-1-yl)phenyl]propionate. which was coupled with 1-naphthyl isocyanate and reduced to provide urea II. In a competition assay with SKF 86002 as a fluorescent probe, II inhibited p38 MAP kinase with IC50 of 45 nM.

L4 ANSWER 2 OF 8 MEDLINE on STN

2004473483. PubMed ID: 15384251. Analysis of vascular endothelial growth factor (VEGF) and a receptor subtype (KDR/flk-1) in the liver of rats exposed to riddelliine: a potential role in the development of hemangiosarcoma. Moyer C; Allen D; Basabe A; Maronpot R R; Nyska A. (Pathology Associates--A Charles River Company, Raleigh, North Carolina, USA.) Experimental and toxicologic pathology : official journal of the Gesellschaft fur Toxikologische Pathologie, (2004 Jul) Vol. 55, No. 6, pp. 455-65. Journal code: 9208920. ISSN: 0940-2993. Pub. country: Germany: Germany, Federal Republic of. Language: English.

AB Riddelliine alters hepatocellular and endothelial cell kinetics and function including stimulating an increase in hepatocytic vascular endothelial growth factor (VEGF) in the absence of increased serological levels of VEGF (NYSKA et al. 2002). The objective of this study was to further assess hepatic VEGF and KDR/flk-1 synthesis and expression by hepatic cells under riddelliine treatment conditions. Forty-two male F344/N rats were dosed by gavage with riddelliine (0, 1.0, and 2.5 mg/kg/day) for 6 weeks. Seven animals/group were sacrificed after 8 consecutive daily doses; remaining rats were terminated after 30 daily doses, excluding weekends. Hepatic tissues were evaluated by immunohistochemistry and in situ hybridization. The results showed that VEGF mRNA expression was observed in control and treated animals; however, qualitative differences were noted. Treated animals exhibited VEGF mRNA in clustered, focal hepatocytes and bile duct epithelium, whereas VEGF mRNA in hepatocytes from vehicle control rats was distributed evenly across all hepatocytes. Results evaluating the distribution of the VEGF cognate receptor, KDR/flk-1 showed that randomly distributed, rare sinusoidal endothelium, including those demonstrating karyomegaly and cytomegaly expressed KDR/flk-1. Phosphorylation of KDR /flk-1 at pTyr996 and pTyr1054/1059, but not pTyr951, was also detected,

evidence that endothelial cell KDR/flk-1 was activated. These results suggest that both hepatocytes and endothelial cells are targets of riddelliine-induced injury. We speculate that damage to both populations of cells may lead to dysregulated VEGF synthesis by hepatocytes and activation of KDR/flk-1 by endothelium leading to the induction of sustained endothelial cell proliferation, culminating in the development of hepatic hemangiosarcoma.

L4 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN
2003:757736 Document No. 139:240839 The use of an epitope of vascular endothelial growth factor receptor KDR/Flk-1 for the screening of KDR/Flk-1-modulating drugs. Cartlidge, Sue Ann (Astrazeneca AB, Swed.; Astrazeneca Uk Limited). PCT Int. Appl. WO 2003078465 A1 20030925, 26 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-GB991 20030311. PRIORITY: GB 2002-6072 20020315.
AB The present invention relates to the use of the epitope which comprises the tyrosine at position 1214 in the amino acid sequence of the vascular endothelial growth factor receptor, KDR/Flk-1, as a marker in the measurement of a change in the activation state of the KDR/Flk-1 receptor and to probes, such as antibodies, which recognize said epitope. The invention also relates to the use of KDR/Flk-1 epitope Y1214 as a marker in the detection of and/or measurement of the level of the KDR/Flk-1 receptor and to assays which utilize the use of the Y1214 epitope and to compds. derived from said assays.

L4 ANSWER 4 OF 8 MEDLINE on STN DUPLICATE 1
2002096864. PubMed ID: 11719508. Reactive oxygen species as downstream mediators of angiogenic signaling by vascular endothelial growth factor receptor-2/KDR. Colavitti Renata; Pani Giovanni; Bedogni Barbara; Anzevino Rosanna; Borrello Silvia; Waltenberger Johannes; Galeotti Tommaso. (Institute of General Pathology, Catholic University Medical School, Rome 00168, Italy.) The Journal of biological chemistry, (2002 Feb 1) Vol. 277, No. 5, pp. 3101-8. Electronic Publication: 2001-11-21. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.
AB Recent evidence shows the involvement of reactive oxygen species (ROS) in the mitogenic cascade initiated by the tyrosine kinase receptors of several growth factor peptides. We have asked whether also the vascular endothelial growth factor (VEGF) utilizes ROS as messenger intermediates downstream of the VEGF receptor-2 (VEGFR-2)/KDR receptor given that the proliferation of endothelial cells during neoangiogenesis is physiologically regulated by oxygen and likely by its derivative species. In porcine aortic endothelial cells stably expressing human KDR, receptor activation by VEGF is followed by a rapid increase in the intracellular generation of hydrogen peroxide as revealed by the peroxide-sensitive probe dichlorofluorescein diacetate. Genetic and pharmacological studies suggest that such oxidant burst requires as upstream events the activation of phosphatidylinositol 3-kinase and the small GTPase Rac-1 and is likely initiated by lipoxygenases. Interestingly, ROS generation in response to VEGF is not blocked but rather potentiated by endothelial nitric-oxide synthase inhibitors diphenyleneiodonium and N(G)methyl-l-arginine, ruling out the possibility of nitric oxide being the oxidant species here detected in VEGF-stimulated cells. Inhibition of KDR-dependent generation of ROS attenuates early signaling events including receptor autophosphorylation and binding to a phospholipase C-gamma-glutathione S-transferase fusion protein. Moreover, catalase, the lipoxygenase inhibitor nordihydroguaiaretic acid,

the synthetic ROS scavenger EUK-134, and phosphatidylinositol 3-kinase inhibitor wortmannin all reduce ERK phosphorylation in response to VEGF, and antioxidants prevent VEGF-dependent mitogenesis. Finally, cell culture and stimulation in a nearly anoxic environment mimic the effect of ROS scavenger on receptor and ERK phosphorylation, reinforcing the idea that ROS are necessary components of the mitogenic signaling cascade initiated by KDR. These data identify ROS as a new class of intracellular angiogenic mediators and may represent a potential premise for new antioxidant-based antiangiogenic therapies.

L4 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN
1998:806801 Document No. 130:62052 Regulatory sequences conferring expression of a heterologous sequence in endothelial cells for therapeutic applications in vascular disease. Breier, Georg; Risau, Werner; Ronicke, Volker (Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V., Germany). PCT Int. Appl. WO 9855638 A1 19981210, 107 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-EP3318 19980603. PRIORITY: EP 1997-108959 19970603.
AB Described are recombinant DNA mols. comprising the regulatory sequence(s) of an intron of the Endothelial Growth Factor (VEGF) receptor-2 gene (Flk-1) or of a gene homologous to the Flk-1 gene, being capable of conferring expression of a heterologous DNA sequence in endothelial cells, preferably in vivo. Vectors comprising said DNA mols. as well as host cells containing the same are provided. Also provided are pharmaceutical and diagnostic compns. comprising such recombinant DNA mols. and vectors. Furthermore, cells and transgenic non-human animals, comprising the aforementioned recombinant DNA mols. or vectors stably integrated into their genome and their use for the identification of substances capable of suppressing or activating transcription of a gene in endothelial cells are described. Described is further the use of the before described recombinant DNA mols. and vectors for the preparation of pharmaceutical compns. for treating, preventing, and/or delaying a vascular or tumorous disease in a subject. Furthermore, uses of the recombinant DNA mols. and vectors of the invention for the preparation of pharmaceutical compns. for inducing a vascular or tumorous disease in a non-human animal are provided.

L4 ANSWER 6 OF 8 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
1998:391320 Document No.: PREV199800391320. Transcription factors Sp1 and Sp3 alter vascular endothelial growth factor receptor expression through a novel recognition sequence. Hata, Yasuaki; Duh, Elia; Zhang, Kang; Robinson, Gregory S.; Aiello, Lloyd Paul [Reprint author]. Joslin Diabetes Cent., One Joslin Place, Boston, MA 02215, USA. Journal of Biological Chemistry, (July 24, 1998) Vol. 273, No. 30, pp. 19294-19303. print. CODEN: JBCHA3. ISSN: 0021-9258. Language: English.
AB Kinase domain receptor (KDR) is a high affinity, endothelial cell-specific, autophosphorylating tyrosine kinase receptor for vascular endothelial growth factor. This transcriptionally regulated receptor is a critical mediator of endothelial cell (EC) growth and vascular development. In this study, we identify a DNA element modulating KDR promoter activity and evaluate the nuclear binding proteins accounting for a portion of the cell-type specificity of the region. KDR promoter luciferase activity was retained within -85/+296 and was 10-30-fold higher in EC than non-EC. Electrophoretic mobility shift assays demonstrated specific nuclear protein binding to -85/-64, and single point mutations suggested important binding nucleotides between -79/-68 with five critical bases between -74/-70 (5'-CTCCT-3'). DNA-protein complexes were displaced by Sp1 consensus sequence oligodeoxynucleotides and supershifted by Sp1- and Sp3-specific antibodies. Sp1 and Sp3 protein in EC nuclear extracts bound the -79/-68

region even when all surrounding classic Sp1 recognition sites were removed. Sp1 protein in nuclear extracts was 4-24-fold higher in EC than non-EC, whereas Sp3 was 3-7-fold higher. Sp1/Sp3 ratios in EC were 2-10-fold higher. Overexpression of Sp1 protein increased KDR promoter activity 3-fold in both EC and non-EC, whereas simultaneous co-expression of Sp3 attenuated this response. An Sp1 consensus sequence cis element 'decoy" reduced EC KDR promoter activity and mRNA expression by 85 and 69%, respectively. An antisense phosphorothioate oligodeoxynucleotide to Sp1 inhibited Sp1 and KDR protein expression by 66 and 68%, respectively, without changing Sp3 protein expression. These data illustrate that Sp1 and Sp3 modulate. KDR promoter activity through a novel recognition binding sequence. However, since Sp1-mediated promoter activation is attenuated by Sp3, endothelial selective KDR promoter activity may be partially regulated by variations in the Sp1/Sp3 ratio.

L4 ANSWER 7 OF 8 MEDLINE on STN DUPLICATE 2

96297928. PubMed ID: 8763741. [Modulation of the tumoral progression by anti-idiotypic antibodies of angiogenesis factors]. Modulation de la progression tumorale par des anticorps anti-idiotypiques de facteurs angiogeniques. Ortega N; Jonca F; Vincent S; Favard C; Malavaud B; Bertrand N; Mazerolles C; Richmann P; Pouliquen Y; Sarrammon J P; Ruchoux M M; Plouet J. (Laboratoire de biologie moleculaire eucaryote, CNRS UPR 9006, Toulouse, France.) Comptes rendus de l'Academie des sciences. Serie III, Sciences de la vie, (1996 May) Vol. 319, No. 5, pp. 411-5. Journal code: 8503078. ISSN: 0764-4469. Pub. country: France. Language: French.

AB We took advantage of the anti-idiotypic strategy to design circulating probes mimicking the biological effects of VEGF (vascular endothelial growth factor) or FGF2 (fibroblast growth factor 2). The activation of the VEGF receptor KDR/flk-1 induced endothelial cell proliferation but not their migration, whereas that of the FGF receptor FGF-R1 gave opposite results. The long lasting delivery of KDR/flk-1 agonists, but not that of FGF-R1, in nude mice grafted with tumor fragments enhanced the tumor volume. Microscopic examination showed an increase in both the vascularization and the proliferation of cancer cells. In contrast, no difference in cell proliferation was observed within normal tissues.

L4 ANSWER 8 OF 8 MEDLINE on STN

95101869. PubMed ID: 7803624. Vascular endothelial growth factor receptor localization and activation in human trophoblast and choriocarcinoma cells. Charnock-Jones D S; Sharkey A M; Boocock C A; Ahmed A; Plevin R; Ferrara N; Smith S K. (Department of Obstetrics and Gynaecology, University of Cambridge, Rosie Maternity Hospital, England.) Biology of reproduction, (1994 Sep) Vol. 51, No. 3, pp. 524-30. Journal code: 0207224. ISSN: 0006-3363. Pub. country: United States. Language: English.

AB Vascular endothelial growth factor (VEGF; also known as vascular permeability factor) is a secreted angiogenic growth factor. It is highly specific for endothelial cells, and its receptor, the fms-like tyrosine kinase (flt), has been localized only to endothelial cells in vivo. Here we describe the expression of mRNA encoding flt in human trophoblast as revealed by in situ hybridization. This mRNA is highly expressed in the cytotrophoblast shell and columns and also highly expressed by the extravillous trophoblast (EVT) in the maternal decidua both in the first trimester and at term. The trophoblast-like choriocarcinoma cell line BeWo also expresses this receptor and the related receptor, kinase domain-containing receptor (KDR), which is also a receptor for VEGF. Treatment of the cell line BeWo with VEGF165 stimulated 3H-thymidine incorporation and tyrosine phosphorylation of MAP (mitogen-activated protein) kinase in a time- and dose-dependent fashion. This study is the first demonstration of the presence of flt on non-endothelial cells in vivo and suggests a role for VEGF in the growth and differentiation of cytotrophoblast at implantation.

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L5 17 L2 AND PHOSPHORYLATION

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L6 9 DUP REMOVE L5 (8 DUPLICATES REMOVED)

=> d l6 1-9 cbib abs

L6 ANSWER 1 OF 9 MEDLINE on STN
2004473483. PubMed ID: 15384251. Analysis of vascular endothelial growth factor (VEGF) and a receptor subtype (KDR/flk-1) in the liver of rats exposed to riddelliine: a potential role in the development of hemangiosarcoma. Moyer C; Allen D; Basabe A; Maronpot R R; Nyska A. (Pathology Associates--A Charles River Company, Raleigh, North Carolina, USA.) Experimental and toxicologic pathology : official journal of the Gesellschaft fur Toxikologische Pathologie, (2004 Jul) Vol. 55, No. 6, pp. 455-65. Journal code: 9208920. ISSN: 0940-2993. Pub. country: Germany: Germany, Federal Republic of. Language: English.
AB Riddelliine alters hepatocellular and endothelial cell kinetics and function including stimulating an increase in hepatocytic vascular endothelial growth factor (VEGF) in the absence of increased serological levels of VEGF (NYSKA et al. 2002). The objective of this study was to further assess hepatic VEGF and KDR/flk-1 synthesis and expression by hepatic cells under riddelliine treatment conditions. Forty-two male F344/N rats were dosed by gavage with riddelliine (0, 1.0, and 2.5 mg/kg/day) for 6 weeks. Seven animals/group were sacrificed after 8 consecutive daily doses; remaining rats were terminated after 30 daily doses, excluding weekends. Hepatic tissues were evaluated by immunohistochemistry and in situ hybridization. The results showed that VEGF mRNA expression was observed in control and treated animals; however, qualitative differences were noted. Treated animals exhibited VEGF mRNA in clustered, focal hepatocytes and bile duct epithelium, whereas VEGF mRNA in hepatocytes from vehicle control rats was distributed evenly across all hepatocytes. Results evaluating the distribution of the VEGF cognate receptor, KDR/flk-1 showed that randomly distributed, rare sinusoidal endothelium, including those demonstrating karyomegaly and cytomegaly expressed KDR/flk-1. Phosphorylation of KDR/flk-1 at pTyr996 and pTyr1054/1059, but not pTyr951, was also detected, evidence that endothelial cell KDR/flk-1 was activated. These results suggest that both hepatocytes and endothelial cells are targets of riddelliine-induced injury. We speculate that damage to both populations of cells may lead to dysregulated VEGF synthesis by hepatocytes and activation of KDR/flk-1 by endothelium leading to the induction of sustained endothelial cell proliferation, culminating in the development of hepatic hemangiosarcoma.

L6 ANSWER 2 OF 9 MEDLINE on STN DUPLICATE 1
2002096864. PubMed ID: 11719508. Reactive oxygen species as downstream mediators of angiogenic signaling by vascular endothelial growth factor receptor-2/KDR. Colavitti Renata; Pani Giovanni; Bedogni Barbara; Anzevino Rosanna; Borrello Silvia; Waltenberger Johannes; Galeotti Tommaso. (Institute of General Pathology, Catholic University Medical School, Rome 00168, Italy.) The Journal of biological chemistry, (2002 Feb 1) Vol. 277, No. 5, pp. 3101-8. Electronic Publication: 2001-11-21. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.
AB Recent evidence shows the involvement of reactive oxygen species (ROS) in the mitogenic cascade initiated by the tyrosine kinase receptors of several growth factor peptides. We have asked whether also the vascular endothelial growth factor (VEGF) utilizes ROS as messenger intermediates downstream of the VEGF receptor-2 (VEGFR-2)/KDR receptor given that the proliferation of endothelial cells during neoangiogenesis is physiologically regulated by oxygen and likely by its derivative species.

In porcine aortic endothelial cells stably expressing human KDR, receptor activation by VEGF is followed by a rapid increase in the intracellular generation of hydrogen peroxide as revealed by the peroxide-sensitive probe dichlorofluorescein diacetate. Genetic and pharmacological studies suggest that such oxidant burst requires as upstream events the activation of phosphatidylinositol 3-kinase and the small GTPase Rac-1 and is likely initiated by lipoxygenases. Interestingly, ROS generation in response to VEGF is not blocked but rather potentiated by endothelial nitric-oxide synthase inhibitors diphenyleneiodonium and N(G)methyl-l-arginine, ruling out the possibility of nitric oxide being the oxidant species here detected in VEGF-stimulated cells. Inhibition of KDR-dependent generation of ROS attenuates early signaling events including receptor autophosphorylation and binding to a phospholipase C-gamma-glutathione S-transferase fusion protein. Moreover, catalase, the lipoxygenase inhibitor nordihydroguaiaretic acid, the synthetic ROS scavenger EUK-134, and phosphatidylinositol 3-kinase inhibitor wortmannin all reduce ERK phosphorylation in response to VEGF, and antioxidants prevent VEGF-dependent mitogenesis. Finally, cell culture and stimulation in a nearly anoxic environment mimic the effect of ROS scavenger on receptor and ERK phosphorylation, reinforcing the idea that ROS are necessary components of the mitogenic signaling cascade initiated by KDR. These data identify ROS as a new class of intracellular angiogenic mediators and may represent a potential premise for new antioxidant-based antiangiogenic therapies.

L6 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN

2001:427336 Document No. 135:41380 Cloning and characterization of a gene for a tyrosine phosphorylation-stimulating ligand, VEGF-C, for the FLT4 receptor tyrosine kinase. Alitalo, Kari; Joukov, Vladimir (Ludwig Institute for Cancer Research, USA; Helsinki University Licensing, Ltd. Oy). U.S. US 6245530 B1 20010612, 68 pp., Cont.-in-part of U.S. Ser. No. 510,133. (English). CODEN: USXXAM. APPLICATION: US 1996-585895 19960112. PRIORITY: US 1995-510133 19950801.

AB Provided are protein and cDNA sequences of a tyrosine phosphorylation-stimulating ligand, VEGF-C, for the receptor tyrosine kinase, Flt4. VEGF-C, a 23 kDa protein that binds the FLT4 receptor tyrosine kinase and stimulates tyrosine phosphorylation of FLT4 is characterized and a cDNA. The ligand is of potential therapeutic use in controlling the proliferation of endothelial cells. The protein was purified from conditioned medium of PC-3 cell culture by affinity chromatog. A cDNA encoding the ligand was cloned by PCR. The cDNA encoded a protein of approx. 47 kDa that appears to be a precursor that is processed via a 32 kDa intermediate to the mature 23 kDa form that forms a dimer. Alternate splicing of the mRNA appears to occur in response to hypoxia. High-level expression of the gene from the K14 keratin promoter in transgenic mice led to abundant growth of lymphatic vessels in the skin. Also provided are vectors encoding the ligands, pharmaceutical compns. and diagnostic reagents.

L6 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN

2000:589930 Document No. 133:191995 Antibodies to Flt4, a receptor tyrosine kinase and uses thereof. Alitalo, Karai; Aprelikova, Olga; Pajusola, Katri; Armstrong, Elina; Korhonen, Jaana; Kaipainen, Arja; Matikainien, Marja-terttu (Orion Corp., Finland; Ludwig Institute for Cancer Research). U.S. US 6107046 A 20000822, 66 pp., Cont.-in-part of U. S. 5,776,755. (English). CODEN: USXXAM. APPLICATION: US 1997-901710 19970728. PRIORITY: US 1992-959951 19921009; US 1994-257754 19940609; US 1994-340011 19941114.

AB The present invention provide purified Flt4 receptor tyrosine kinase polypeptides and fragments thereof, polynucleotides encoding such polypeptides, antibodies that specifically bind such polypeptides, and uses therefor. The polypeptides and antibodies are useful for detecting lymphatic vessels; and for monitoring inflammation, infection, traumas, growth and immunol. disorders of lymphatic vessels.

L6 ANSWER 5 OF 9 MEDLINE on STN DUPLICATE 2
2000183929. PubMed ID: 10688880. Identification of a natural soluble neuropilin-1 that binds vascular endothelial growth factor: In vivo expression and antitumor activity. Gagnon M L; Bielenberg D R; Gechtman Z; Miao H Q; Takashima S; Soker S; Klagsbrun M. (Departments of Surgical Research, Pathology, and Urology, Children's Hospital and Harvard Medical School, 300 Longwood Avenue, Boston, MA 02115, USA.) Proceedings of the National Academy of Sciences of the United States of America, (2000 Mar 14) Vol. 97, No. 6, pp. 2573-8. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB Neuropilin-1 (NRP1) is a 130-kDa transmembrane receptor for semaphorins, mediators of neuronal guidance, and for vascular endothelial growth factor 165 (VEGF(165)), an angiogenesis factor. A 2.2-kb truncated NRP1 cDNA was cloned that encodes a 644-aa soluble NRP1 (sNRP1) isoform containing just the a/CUB and b/coagulation factor homology extracellular domains of NRP1. sNRP1 is secreted by cells as a 90-kDa protein that binds VEGF(165), but not VEGF(121). It inhibits (125)I-VEGF(165) binding to endothelial and tumor cells and VEGF(165)-induced tyrosine phosphorylation of KDR in endothelial cells. The 3' end of sNRP1 cDNA contains a unique, 28-bp intron-derived sequence that is absent in full-length NRP1 cDNA. Using a probe corresponding to this unique sequence, sNRP1 mRNA could be detected by in situ hybridization differentially from full-length NRP1 mRNA, for example, in cells of liver, kidney, skin, and breast. Analysis of blood vessels in situ showed that NRP1, but not sNRP1, was expressed. sNRP1 was functional in vivo. Unlike control tumors, tumors of rat prostate carcinoma cells expressing recombinant sNRP1 were characterized by extensive hemorrhage, damaged vessels, and apoptotic tumor cells. These results demonstrate the existence of a naturally occurring, soluble NRP1 that is expressed differently from intact NRP1 and that appears to be a VEGF(165) antagonist.

L6 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN
1998:747594 Document No. 130:22238 Enzymic ribozyme treatment of diseases or cancers related to expression of c-raf gene. Jarvis, Thale; Matulic-Adamic, Jasenka; Reynolds, Mark; Kisich, Kevin; Bellon, Laurent; Parry, Tom; Beigelman, Leonid; McSwiggen, James A.; Karpeisky, Alexander; Burgin, Alex; Thompson, James; Workman, Christopher T.; Beaudry, Amber; Sweedler, David (Ribozyme Pharmaceuticals, Inc., USA; et al.). PCT Int. Appl. WO 9850530 A2 19981112, 259 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US9249 19980505. PRIORITY: US 1997-46059 19970509; US 1997-49002 19970609; US 1997-51718 19970703; US 1997-56808 19970822; US 1997-61324 19971002; US 1997-61321 19971002; US 1997-64866 19971105; US 1997-68212 19971219.

AB This invention relates to identification, synthesis and use of nucleic acid catalysts to cleave RNA species that are required for cellular growth responses. In particular, the invention describes the selection and function of ribozymes capable of cleaving RNA encoded by c-raf gene. Such ribozymes may be used to inhibit the proliferation of tumor cells in one or more cancers, restenosis, psoriasis, fibrosis and rheumatoid arthritis.

L6 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN
1997:240615 Document No. 126:221078 A tyrosine phosphorylation -stimulating ligand, VEGF-C, for the FLT4 receptor tyrosine kinase and a cDNA encoding it. Alitalo, Kari; Joukov, Vladimir (Helsinki University Licensing Ltd. Oy, Finland). PCT Int. Appl. WO 9705250 A2 19970213, 183 pp. DESIGNATED STATES: W: AU, CA, CN, JP, NO, NZ, US; RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1996-FI427 19960801. PRIORITY: US 1995-510133 19950801; US 1996-585895 19960112; US 1996-601132 19960214; US

1996-671573 19960628.

AB VEGF-C, a 23 kDa protein that binds the FLT4 receptor tyrosine kinase and stimulates tyrosine phosphorylation of FLT4 is characterized and a cDNA. The ligand is of potential therapeutic use in controlling the proliferation of endothelial cells. The protein was purified from conditioned medium of PC-3 cell culture by affinity chromatog. A cDNA encoding the ligand was cloned by PCR. The cDNA encoded a protein of approx. 47 kDa that appears to be a precursor that is processed via a 32 kDa intermediate to the mature 23 kDa form that forms a dimer. Alternate splicing of the mRNA appears to occur in response to hypoxia. High-level expression of the gene from the K14 keratin promoter in transgenic mice led to abundant growth of lymphatic vessels in the skin.

L6 ANSWER 8 OF 9 MEDLINE on STN

94336223. PubMed ID: 8058332. A new communication system between hepatocytes and sinusoidal endothelial cells in liver through vascular endothelial growth factor and Flt tyrosine kinase receptor family (Flt-1 and KDR/Flk-1). Yamane A; Seetharam L; Yamaguchi S; Gotoh N; Takahashi T; Neufeld G; Shibuya M. (Department of Genetics, University of Tokyo, Japan.) Oncogene, (1994 Sep) Vol. 9, No. 9, pp. 2683-90. Journal code: 8711562. ISSN: 0950-9232. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Hepatocyte Growth Factor (HGF)/Scatter Factor secreted from sinusoidal endothelial cells and Kupffer cells in liver activates the c-Met tyrosine kinase receptor expressed on hepatocytes. Here we report yet another possible communication system through a different ligand and tyrosine kinase receptor in an opposite direction. We isolated and determined the primary structure of the entire coding region of rat flt-1 (fms-like tyrosine kinase), a receptor for Vascular Endothelial Growth Factor (VEGF). Using rat flt-1 cDNA as a probe we found that the flt-1 mRNA was expressed at very high levels in sinusoidal endothelial cells in normal rat liver, but was hardly detectable in hepatocytes. The transcripts of another VEGF receptor KDR/Flk-1 structurally related to Flt-1 was also expressed specifically in sinusoidal endothelial cells. On the other hand, VEGF mRNA was expressed weakly in hepatocytes, but not in the nonparenchymal cell fraction. Furthermore, in an in vitro culture system, VEGF demonstrated a remarkably specific growth-stimulatory activity as well as maintenance activity on the sinusoidal endothelial cells. These results suggest that hepatocytes regulate the proliferation and survival of the sinusoidal endothelial cells in liver in a paracrine manner. Therefore two reciprocal communication systems, VEGF-Flt receptor family and HGF-Met receptor, may exist in hepatic tissue.

L6 ANSWER 9 OF 9 MEDLINE on STN

95101869. PubMed ID: 7803624. Vascular endothelial growth factor receptor localization and activation in human trophoblast and choriocarcinoma cells. Charnock-Jones D S; Sharkey A M; Boocock C A; Ahmed A; Plevin R; Ferrara N; Smith S K. (Department of Obstetrics and Gynaecology, University of Cambridge, Rosie Maternity Hospital, England.) Biology of reproduction, (1994 Sep) Vol. 51, No. 3, pp. 524-30. Journal code: 0207224. ISSN: 0006-3363. Pub. country: United States. Language: English.

AB Vascular endothelial growth factor (VEGF; also known as vascular permeability factor) is a secreted angiogenic growth factor. It is highly specific for endothelial cells, and its receptor, the fms-like tyrosine kinase (flt), has been localized only to endothelial cells in vivo. Here we describe the expression of mRNA encoding flt in human trophoblast as revealed by in situ hybridization. This mRNA is highly expressed in the cytotrophoblast shell and columns and also highly expressed by the extravillous trophoblast (EVT) in the maternal decidua both in the first trimester and at term. The trophoblast-like choriocarcinoma cell line BeWo also expresses this receptor and the related receptor, kinase domain-containing receptor (KDR), which is also a receptor for VEGF. Treatment of the cell line BeWo with VEGF165 stimulated 3H-thymidine incorporation and tyrosine phosphorylation of MAP (mitogen-activated protein) kinase in a time- and dose-dependent fashion.

This study is the first demonstration of the presence of flt on non-endothelial cells in vivo and suggests a role for VEGF in the growth and differentiation of cytotrophoblast at implantation.

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The file names of duplicates that can be kept are listed above.
Please enter one of these file names.

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L8 ANSWER 1 OF 9 MEDLINE on STN
2004473483. PubMed ID: 15384251. Analysis of vascular endothelial growth factor (VEGF) and a receptor subtype (KDR/flk-1) in the liver of rats exposed to riddelliine: a potential role in the development of hemangiosarcoma. Moyer C; Allen D; Basabe A; Maronpot R R; Nyska A. (Pathology Associates--A Charles River Company, Raleigh, North Carolina, USA.) Experimental and toxicologic pathology : official journal of the Gesellschaft fur Toxikologische Pathologie, (2004 Jul) Vol. 55, No. 6, pp. 455-65. Journal code: 9208920. ISSN: 0940-2993. Pub. country: Germany: Germany, Federal Republic of. Language: English.
AB Riddelliine alters hepatocellular and endothelial cell kinetics and function including stimulating an increase in hepatocytic vascular endothelial growth factor (VEGF) in the absence of increased serological levels of VEGF (NYSKA et al. 2002). The objective of this study was to further assess hepatic VEGF and KDR/flk-1 synthesis and expression by hepatic cells under riddelliine treatment conditions. Forty-two male F344/N rats were dosed by gavage with riddelliine (0, 1.0, and 2.5 mg/kg/day) for 6 weeks. Seven animals/group were sacrificed after 8 consecutive daily doses; remaining rats were terminated after 30 daily doses, excluding weekends. Hepatic tissues were evaluated by immunohistochemistry and in situ hybridization. The results showed that VEGF mRNA expression was observed in control and treated animals; however, qualitative differences were noted. Treated animals exhibited VEGF mRNA in clustered, focal hepatocytes and bile duct epithelium, whereas VEGF mRNA in hepatocytes from vehicle control rats was distributed evenly across all hepatocytes. Results evaluating the distribution of the VEGF cognate receptor, KDR/flk-1 showed that randomly distributed, rare sinusoidal endothelium, including those demonstrating karyomegaly and cytomegaly expressed KDR/flk-1. Phosphorylation of KDR/flk-1 at pTyr996 and pTyr1054/1059, but not pTyr951, was also detected, evidence that endothelial cell KDR/flk-1 was activated. These results suggest that both hepatocytes and endothelial cells are targets of riddelliine-induced injury. We speculate that damage to both populations of cells may lead to dysregulated VEGF synthesis by hepatocytes and activation of KDR/flk-1 by endothelium leading to the induction of sustained endothelial cell proliferation, culminating in the development of hepatic hemangiosarcoma.

L8 ANSWER 2 OF 9 MEDLINE on STN
96297928. PubMed ID: 8763741. [Modulation of the tumoral progression by anti-idiotypic antibodies of angiogenesis factors]. Modulation de la progression tumorale par des anticorps anti-idiotypiques de facteurs

angiogeniques. Ortega N; Jonca F; Vincent S; Favard C; Malavaud B; Bertrand N; Mazerolles C; Richmann P; Pouliquen Y; Sarrammon J P; Ruchoux M M; Plouet J. (Laboratoire de biologie moleculaire eucaryote, CNRS UPR 9006, Toulouse, France.) Comptes rendus de l'Academie des sciences. Serie III, Sciences de la vie, (1996 May) Vol. 319, No. 5, pp. 411-5. Journal code: 8503078. ISSN: 0764-4469. Pub. country: France. Language: French.

AB We took advantage of the anti-idiotypic strategy to design circulating probes mimicking the biological effects of VEGF (vascular endothelial growth factor) or FGF2 (fibroblast growth factor 2). The activation of the VEGF receptor KDR/flk-1 induced endothelial cell proliferation but not their migration, whereas that of the FGF receptor FGF-R1 gave opposite results. The long lasting delivery of KDR/flk-1 agonists, but not that of FGF-R1, in nude mice grafted with tumor fragments enhanced the tumor volume. Microscopic examination showed an increase in both the vascularization and the proliferation of cancer cells. In contrast, no difference in cell proliferation was observed within normal tissues.

L8 ANSWER 3 OF 9 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

96182273 EMBASE Document No.: 1996182273. [Modulation of tumor progression by anti-idiotypic antibodies of angiogenic factors]. MODULATION DE LA PROGRESSION TUMORALE PAR DES ANTICORPS ANTI-IDIOTYPIQUES DE FACTURES ANGIOGENIQUES. Ortega N.; Jonica F.; Vincent S.; Favard C.; Malavaud B.; Bertrand N.; Mazerolles C.; Rischmann P.; Pouliquen Y.; Sarrammon J.P.; Ruchoux M.M.; Plouet J.. Lab de bio moleculaire eucaryote, CNRS UPR 9006, 118, route de Narbonne,31062 Toulouse, France. Comptes Rendus de l'Academie des Sciences - Serie III Vol. 319, No. 5, pp. 411-415 1996. ISSN: 0764-4469. CODEN: CRASEV
Pub. Country: France. Language: French. Summary Language: French; English.
Entered STN: 960708. Last Updated on STN: 960708

AB We took advantage of the anti-idiotypic strategy to design circulating probes mimicking the biological effects of VEGF (vascular endothelial growth factor) or FGF2 (fibroblast growth factor 2). The activation of the VEGF receptor KDR/flk-1 induced endothelial cell proliferation but not their migration, whereas that of the FGF receptor FGF-R1 gave opposite results. The long lasting delivery of KDR/flk-1 agonists, but not that of FGF-R1, in nude mice grafted with tumor fragments enhanced the tumor volume. Microscopic examination showed an increase in both the vascularization and the proliferation of cancer cells. In contrast, no difference in cell proliferation was observed within normal tissues.

L8 ANSWER 4 OF 9 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

1996:367890 Document No.: PREV199699090246. Modulation of tumor progression by anti-idiotypic antibodies of angiogenic factors. Ortega, Nathalie; Jonca, Frederic; Vincent, Sylvie; Favard, Catherine; Malavaud, Bernard; Bertrand, Nicolas; Mazerolles, Chaterine; Rischmann, Pascal; Pouliquen, Yves; Sarrammon, Jean-Pierre; Ruchoux, Marie Madeleine; Plouet, Jean [Reprint author]. Lab. de Biol. Mol. Euaryote, CNRS UPR 9006, 118 Route de Narbonne, 31062 Toulouse, France. Comptes Rendus de l'Academie des Sciences Serie III Sciences de la Vie, (1996) Vol. 319, No. 5, pp. 411-415.
CODEN: CRASEV. ISSN: 0764-4469. Language: French.

AB We took advantage of the anti-idiotypic strategy to design circulating probes mimicking the biological effects of VEGF (vascular endothelial growth factor) or FGF2 (fibroblast growth factor 2). The activation of the VEGF receptor KDR/flk-1 induced endothelial cell proliferation but not their migration, whereas that of the FGF receptor FGF-R1 gave opposite results. The long lasting delivery of KDR/flk-1 agonists, hut not that of FGF-R1, in nude mice grafted with tumor fragments enhanced the tumor volume. Microscopic examination showed an increase in both the vascularization and the proliferation of cancer cells. In contrast, no difference in cell proliferation was observed within normal tissues.

L8 ANSWER 5 OF 9 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

1996:456941 The Genuine Article (R) Number: UR341. Modulation of tumor progression by anti-idiotypic antibodies of angiogenic factors. Ortega N (Reprint); Jonca F; Vincent S; Favard C; Malavaud B; Bertrand N; Mazerolles C; Rischmann P; Pouliquen Y; Sarrammon J P; Ruchoux M M; Plouet J. LAB BIOL MOL EUCARYOTE, CNRS UPR 9006, F-31062 TOULOUSE, FRANCE; HOP LILLE, NEUROPATHOL LAB, F-59037 LILLE, FRANCE; HOP PURPAN, CTR CLAUDE BERNARD CHIRURG EXPT, F-31059 TOULOUSE, FRANCE; HOP HOTEL DIEU, INSERM U86, F-75004 PARIS, FRANCE; HOP PURPAN, ANAT PATHOL LAB, F-31059 TOULOUSE, FRANCE. COMPTES RENDUS DE L ACADEMIE DES SCIENCES SERIE III-SCIENCES DE LA VIE-LIFE SCIENCES (MAY 1996) Vol. 319, No. 5, pp. 411-415. ISSN: 0764-4469 . Publisher: JOHN LIBBEY EUROTEXT LTD, 127 AVE DE LA REPUBLIQUE, 92120 MONTROUGE, FRANCE. Language: French.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We took advantage of the anti-idiotypic strategy to design circulating probes mimicking the biological effects of VEGF (vascular endothelial growth factor) or FGF2 (fibroblast growth factor 2). The activation of the VEGF receptor KDR/flk-1 induced endothelial cell proliferation but not their migration, whereas that of the FGF receptor FGF-RI gave opposite results. The long lasting delivery of KDR/flk-1 agonists, but not that of FGF-R1, in nude mice grafted with tumor fragments enhanced the tumor volume. Microscopic examination showed an increase in both the vascularization and the proliferation of cancer cells. In contrast no difference in cell proliferation was observed within normal tissues.

L8 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN

2003:757736 Document No. 139:240839 The use of an epitope of vascular endothelial growth factor receptor KDR/Flk-1 for the screening of KDR/Flk-1-modulating drugs. Cartlidge, Sue Ann (Astrazeneca AB, Swed.; Astrazeneca Uk Limited). PCT Int. Appl. WO 2003078465 A1 20030925, 26 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-GB991 20030311. PRIORITY: GB 2002-6072 20020315.

AB The present invention relates to the use of the epitope which comprises the tyrosine at position 1214 in the amino acid sequence of the vascular endothelial growth factor receptor, KDR/Flk-1, as a marker in the measurement of a change in the activation state of the KDR/Flk-1 receptor and to probes, such as antibodies, which recognize said epitope. The invention also relates to the use of KDR/Flk-1 epitope Y1214 as a marker in the detection of and/or measurement of the level of the KDR/Flk-1 receptor and to assays which utilize the use of the Y1214 epitope and to compds. derived from said assays.

L8 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN

2001:185593 Document No. 134:218029 Kaposi's sarcoma-associated herpesvirus KS-SM gene and protein and uses thereof. Swaminathan, Sankar (Board of Regents, the University of Texas System, USA). PCT Int. Appl. WO 2001017552 A1 20010315, 26 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE,

NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US24698 20000908. PRIORITY: US 1999-PV153092 19990909.

AB Kaposi's sarcoma-associated herpesvirus (KSHV) is also known as human herpesvirus 8 (HHV8). The present invention disclosed a new gene cloned from human cells infected with HHV8 and designated KS-SM. The KS-SM is predicted to encode a 455 amino acid protein with 35% similarity to the EBV SM and HSV ICP37 proteins. The KS-SM protein localizes to the nucleus of infected cells and was found to enhance the level of expression of certain cotransfected genes, such as a vascular endothelial growth factor receptor gene, known as KDK/flk-1, but not other genes (luciferase). These effects seem to be mediated at the post-transcriptional level. The discovery of KS-SM gene provides a target for pharmaceutical agents for treatment of Kaposi's sarcoma.

L8 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN

1998:806801 Document No. 130:62052 Regulatory sequences conferring expression of a heterologous sequence in endothelial cells for therapeutic applications in vascular disease. Breier, Georg; Risau, Werner; Ronicke, Volker (Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V., Germany). PCT Int. Appl. WO 9855638 A1 19981210, 107 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-EP3318 19980603. PRIORITY: EP 1997-108959 19970603.

AB Described are recombinant DNA mols. comprising the regulatory sequence(s) of an intron of the Endothelial Growth Factor (VEGF) receptor-2 gene (Flk-1) or of a gene homologous to the Flk-1 gene, being capable of conferring expression of a heterologous DNA sequence in endothelial cells, preferably in vivo. Vectors comprising said DNA mols. as well as host cells containing the same are provided. Also provided are pharmaceutical and diagnostic compns. comprising such recombinant DNA mols. and vectors. Furthermore, cells and transgenic non-human animals, comprising the aforementioned recombinant DNA mols. or vectors stably integrated into their genome and their use for the identification of substances capable of suppressing or activating transcription of a gene in endothelial cells are described. Described is further the use of the before described recombinant DNA mols. and vectors for the preparation of pharmaceutical compns. for treating, preventing, and/or delaying a vascular or tumorous disease in a subject. Furthermore, uses of the recombinant DNA mols. and vectors of the invention for the preparation of pharmaceutical compns. for inducing a vascular or tumorous disease in a non-human animal are provided.

L8 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN

1996:432246 Document No. 125:111528 Modulation of tumor progression by anti-idiotypic antibodies of angiogenic factors. Ortega, Nathalie; Jonca, Frederic; Vincent, Sylvie; Favard, Catherine; Malavaud, Bernard; Bertrand, Nicolas; Mazerolles, Catherine; Rischmann, Pascal; Pouliquen, Yves; et al. (Laboratoire de biologie moleculaire eucaryote, CNRS, Toulouse, 31062, Fr.). Comptes Rendus de l'Academie des Sciences, Serie III: Sciences de la Vie, 319(5), 411-415 (French) 1996. CODEN: CRASEV. ISSN: 0764-4469. Publisher: Libbey Eurotext.

AB The authors took advantage of the anti-idiotypic strategy to design circulating probes mimicking the biol. effects of VEGF (vascular endothelial growth factor) or FGF2 (fibroblast growth factor 2). The activation of the VEGF receptor KDR/flk-1 induced endothelial cell proliferation but not their migration, whereas that of the FGF receptor FGF-R1 gave opposite results. The long lasting delivery of KDR/flk-1 agonists, but not that of FGF-R1, in nude mice grafted with tumor fragments enhanced the tumor volume Microscopic examination showed an increase in both the vascularization and the

proliferation of cancer cells. In contrast, no difference in cell proliferation was observed within normal tissues.

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L10 ANSWER 1 OF 3 MEDLINE on STN
2004473483. PubMed ID: 15384251. Analysis of vascular endothelial growth factor (VEGF) and a receptor subtype (KDR/flk-1) in the liver of rats exposed to riddelliine: a potential role in the development of hemangiosarcoma. Moyer C; Allen D; Basabe A; Maronpot R R; Nyska A. (Pathology Associates--A Charles River Company, Raleigh, North Carolina, USA.) Experimental and toxicologic pathology : official journal of the Gesellschaft fur Toxikologische Pathologie, (2004 Jul) Vol. 55, No. 6, pp. 455-65. Journal code: 9208920. ISSN: 0940-2993. Pub. country: Germany: Germany, Federal Republic of. Language: English.
AB Riddelliine alters hepatocellular and endothelial cell kinetics and function including stimulating an increase in hepatocytic vascular endothelial growth factor (VEGF) in the absence of increased serological levels of VEGF (NYSKA et al. 2002). The objective of this study was to further assess hepatic VEGF and KDR/flk-1 synthesis and expression by hepatic cells under riddelliine treatment conditions. Forty-two male F344/N rats were dosed by gavage with riddelliine (0, 1.0, and 2.5 mg/kg/day) for 6 weeks. Seven animals/group were sacrificed after 8 consecutive daily doses; remaining rats were terminated after 30 daily doses, excluding weekends. Hepatic tissues were evaluated by immunohistochemistry and in situ hybridization. The results showed that VEGF mRNA expression was observed in control and treated animals; however, qualitative differences were noted. Treated animals exhibited VEGF mRNA in clustered, focal hepatocytes and bile duct epithelium, whereas VEGF mRNA in hepatocytes from vehicle control rats was distributed evenly across all hepatocytes. Results evaluating the distribution of the VEGF cognate receptor, KDR/flk-1 showed that randomly distributed, rare sinusoidal endothelium, including those demonstrating karyomegaly and cytomegaly expressed KDR/flk-1. Phosphorylation of KDR/flk-1 at pTyr996 and pTyr1054/1059, but not pTyr951, was also detected, evidence that endothelial cell KDR/flk-1 was activated. These results suggest that both hepatocytes and endothelial cells are targets of riddelliine-induced injury. We speculate that damage to both populations of cells may lead to dysregulated VEGF synthesis by hepatocytes and activation of KDR/flk-1 by endothelium leading to the induction of sustained endothelial cell proliferation, culminating in the development of hepatic hemangiosarcoma.

L10 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN
1998:747594 Document No. 130:22238 Enzymic ribozyme treatment of diseases or cancers related to expression of c-raf gene. Jarvis, Thale; Matulic-Adamic, Jasenka; Reynolds, Mark; Kisich, Kevin; Bellon, Laurent; Parry, Tom; Beigelman, Leonid; McSwiggen, James A.; Karpeisky, Alexander; Burgin, Alex; Thompson, James; Workman, Christopher T.; Beaudry, Amber; Sweedler, David (Ribozyme Pharmaceuticals, Inc., USA; et al.). PCT Int. Appl. WO 9850530 A2 19981112, 259 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK,

ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US9249 19980505. PRIORITY: US 1997-46059 19970509; US 1997-49002 19970609; US 1997-51718 19970703; US 1997-56808 19970822; US 1997-61324 19971002; US 1997-61321 19971002; US 1997-64866 19971105; US 1997-68212 19971219.

AB This invention relates to identification, synthesis and use of nucleic acid catalysts to cleave RNA species that are required for cellular growth responses. In particular, the invention describes the selection and function of ribozymes capable of cleaving RNA encoded by c-raf gene. Such ribozymes may be used to inhibit the proliferation of tumor cells in one or more cancers, restenosis, psoriasis, fibrosis and rheumatoid arthritis.

L10 ANSWER 3 OF 3 MEDLINE on STN

94336223. PubMed ID: 8058332. A new communication system between hepatocytes and sinusoidal endothelial cells in liver through vascular endothelial growth factor and Flt tyrosine kinase receptor family (Flt-1 and KDR/Flk-1). Yamane A; Seetharam L; Yamaguchi S; Gotoh N; Takahashi T; Neufeld G; Shibuya M. (Department of Genetics, University of Tokyo, Japan.) Oncogene, (1994 Sep) Vol. 9, No. 9, pp. 2683-90. Journal code: 8711562. ISSN: 0950-9232. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Hepatocyte Growth Factor (HGF)/Scatter Factor secreted from sinusoidal endothelial cells and Kupffer cells in liver activates the c-Met tyrosine kinase receptor expressed on hepatocytes. Here we report yet another possible communication system through a different ligand and tyrosine kinase receptor in an opposite direction. We isolated and determined the primary structure of the entire coding region of rat flt-1 (fms-like tyrosine kinase), a receptor for Vascular Endothelial Growth Factor (VEGF). Using rat flt-1 cDNA as a probe we found that the flt-1 mRNA was expressed at very high levels in sinusoidal endothelial cells in normal rat liver, but was hardly detectable in hepatocytes. The transcripts of another VEGF receptor KDR/Flk-1 structurally related to Flt-1 was also expressed specifically in sinusoidal endothelial cells. On the other hand, VEGF mRNA was expressed weakly in hepatocytes, but not in the nonparenchymal cell fraction. Furthermore, in an in vitro culture system, VEGF demonstrated a remarkably specific growth-stimulatory activity as well as maintenance activity on the sinusoidal endothelial cells. These results suggest that hepatocytes regulate the proliferation and survival of the sinusoidal endothelial cells in liver in a paracrine manner. Therefore two reciprocal communication systems, VEGF-Flt receptor family and HGF-Met receptor, may exist in hepatic tissue.

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=> s antibod?
L11    2882174 ANTIBOD?

=> s l11 and KDR
L12       1368 L11 AND KDR

=> s l12 and tyrosine
L13        596 L12 AND TYROSINE

=> s l13 and activation
L14        170 L13 AND ACTIVATION

=> s l14 and 1215
L15          0 L14 AND 1215

=> s l14 and 1214
L16          1 L14 AND 1214

=> d l16 cbib abs

L16  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2006 ACS on STN
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2003:757736 Document No. 139:240839 The use of an epitope of vascular endothelial growth factor receptor KDR/Flk-1 for the screening of KDR/Flk-1-modulating drugs. Cartlidge, Sue Ann (Astrazeneca AB, Swed.; Astrazeneca Uk Limited). PCT Int. Appl. WO 2003078465 A1 20030925, 26 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-GB991 20030311. PRIORITY: GB 2002-6072 20020315.

AB The present invention relates to the use of the epitope which comprises the tyrosine at position 1214 in the amino acid sequence of the vascular endothelial growth factor receptor, KDR /Flk-1, as a marker in the measurement of a change in the activation state of the KDR/Flk-1 receptor and to probes, such as antibodies, which recognize said epitope. The invention also relates to the use of KDR/Flk-1 epitope Y1214 as a marker in the detection of and/or measurement of the level of the KDR/Flk-1 receptor and to assays which utilize the use of the Y1214 epitope and to compds. derived from said assays.

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=> s l14 and CDPKFHYDNTAGIS
L17           0 L14 AND CDPKFHYDNTAGIS

=> s l14 and CDPKFHYDNTAGIS
L18           0 L14 AND CDPKFHYDNTAGIS

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     (FILE 'HOME' ENTERED AT 10:58:11 ON 15 NOV 2006)

     FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 10:58:36 ON
     15 NOV 2006
L1         971735 S PROBE
L2            145 S L1 AND KDR
L3             16 S L2 AND ACTIVATION
L4              8 DUP REMOVE L3 (8 DUPLICATES REMOVED)
L5             17 S L2 AND PHOSPHORYLATION
L6              9 DUP REMOVE L5 (8 DUPLICATES REMOVED)
L7             67 S L1 AND FLK-1
L8              9 S L7 AND ACTIVATION
L9              3 S L7 AND PHOSPHORYLATION
L10             3 DUP REMOVE L9 (0 DUPLICATES REMOVED)
L11       2882174 S ANTIBOD?
L12          1368 S L11 AND KDR
L13           596 S L12 AND TYROSINE
L14           170 S L13 AND ACTIVATION
L15             0 S L14 AND 1215
L16             1 S L14 AND 1214
L17             0 S L14 AND CDPKFHYDNTAGIS
L18             0 S L14 AND CDPKFHYDNTAGIS

=> dup remove l14
PROCESSING COMPLETED FOR L14
L19            74 DUP REMOVE L14 (96 DUPLICATES REMOVED)

=> s l19 and receptor tyrosine
L20            9 L19 AND RECEPTOR TYROSINE

=> dup remove l20
PROCESSING COMPLETED FOR L20
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L21 9 DUP REMOVE L20 (0 DUPLICATES REMOVED)

=> d l21 1-9 cbib abs

L21 ANSWER 1 OF 9 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

2006:566932 The Genuine Article (R) Number: 050AR. Vascular endothelial growth factor (VEGF)-receptor2: Its biological functions, major signaling pathway, and specific ligand VEGF-E. Shibuya M (Reprint). Univ Tokyo, Inst Med Sci, Div Genet, Minato Ku, 4-6-1 Shirokane Dai, Tokyo 1088639, Japan (Reprint); Univ Tokyo, Inst Med Sci, Div Genet, Minato Ku, Tokyo 1088639, Japan. shibuya@ims.u-tokyo.ac.jp. ENDOTHELIUM-JOURNAL OF ENDOTHELIAL CELL RESEARCH (MAR-APR 2006) Vol. 13, No. 2, pp. 63-69. ISSN: 1062-3329. Publisher: TAYLOR & FRANCIS INC, 325 CHESTNUT ST, SUITE 800, PHILADELPHIA, PA 19106 USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Two high-affinity receptors for vascular endothelial growth factor (VEGF)-A, VEGFR1 and VEGFR2, cooperate for physiological vasculogenesis and angiogenesis in embryogenesis. VEGFR2 transduces the major signals for angiogenesis via its strong tyrosine kinase activity. However, unlike other representative tyrosine kinase receptors, VEGFR2 does not use the Ras pathway as a major downstream signaling but rather uses the phospholipase C-protein kinase C pathway to signal mitogen-activated protein (MAP)-kinase activation and DNA synthesis. Cell migration signals from VEGFR2 were recently shown to use, at least partly, a pathway dependent on the adaptor molecule TSAd from the kinase-insert region of VEGFR2. VEGFR2 is a direct and major signal transducer for pathological angiogenesis, including cancer and diabetic retinopathy, in cooperation with many other signaling partners; thus, VEGFR2 and its downstream signaling appear to be critical targets for the suppression of these diseases. More than 10 antagonists of VEGFR2, including kinase inhibitors and neutralizing antibodies, are now under clinical trials. Recently, the VEGFR2-specific ligand VEGF-E (also known as Orf-VEGF) family was extensively characterized. Interestingly, activation of VEGFR2 via VEGF-E in vivo results in a strong angiogenic response in mice, with minor effects on inflammation and hypervascular permeability compared with VEGF-A, suggesting that VEGF-E is a useful tool for proangiogenic therapy in ischemic diseases.

L21 ANSWER 2 OF 9 MEDLINE on STN

2005122569. PubMed ID: 15753992. Comparison of the prognosis indication of VEGFR-1 and VEGFR-2 and Tie2 receptor expression in breast carcinoma. Meunier-Carpentier Severine; Dales Jean-Philippe; Djemli Amina; Garcia Stephane; Bonnier Pascal; Andrac-Meyer Lucile; Lavaut Marie-Noelle; Allasia Claude; Charpin Colette. (Department of Pathology, Hopital Nord, Universite de la Mediterranee, Boulevard Pierre Dramard, 13916 Marseille, France.. severine.meunier-carpentier@ap-hm.fr) . International journal of oncology, (2005 Apr) Vol. 26, No. 4, pp. 977-84. Journal code: 9306042. ISSN: 1019-6439. Pub. country: Greece. Language: English.

AB The degree of angiogenesis in breast cancer has previously been shown to be an indicator of prognosis, and tumor microvasculature is a candidate target for new antiangiogenic therapies. The aim of this study was to investigate the prognostic value of vascular endothelial growth factor (VEGF) receptors, VEGFR-1 (Flt-1) and VEGFR-2 (KDR/Flk-1), and Tie2/tek receptor tyrosine kinase in breast carcinoma. VEGF receptors and Tie2 expression was investigated using immunohistochemical assays with monoclonal antibodies on frozen sections in a series of 918 and 909 patients respectively. VEGFR-1 and VEGFR-2 and Tie2 were correlated with long-term (median, 11.3 years) patients' outcome. Univariate (Kaplan-Meier) analysis showed that VEGFR-1 positive tumor surface (cutoff = 5%) was significantly correlated with high metastasis risk (p=0.03) and relapse (p<0.01) in all patients, and in those with node negative tumors (p<0.001 and p<0.01 respectively), but not with overall survival. In contrast Tie2 positive tumor surface (cutoff = 7%) was significantly correlated with poor overall survival (p=0.025) and

also with high metastasis risk particularly among node negative patients ($p<0.01$). Moreover, Tie2 immunoexpression was significantly predictive of relapse ($p=0.003$) in the node negative subgroup ($p=0.02$). In multivariate analysis (Cox model), VEGFR-1 and Tie2 immunoexpressions were identified as independent prognostic indicators. In contrast, univariate analysis showed that VEGFR-2 positive tumor surface (cutoff = 10%) was not correlated with survival or with metastasis and relapse risk. Our results suggest that VEGFR-1 and Tie2 immunohistochemical expression permits the identification of patients with poor outcome, and particularly node negative ones with a high risk for metastasis and relapse. VEGFR-1 and Tie2 immunodetection may also be considered as potential tools for selecting patients who could benefit in the future from specific antiangiogenic therapy interfering with VEGFR-1 and Tie2 activation pathways.

L21 ANSWER 3 OF 9 MEDLINE on STN

2004331823. PubMed ID: 15183893. Vascular endothelial growth factor receptor-1 and receptor-2 initiate a phosphatidylinositide 3-kinase-dependent clonogenic response in acute myeloid leukemia cells. List Alan F; Glinsmann-Gibson Betty; Stadheim Chad; Meuillet Emmanuelle J; Bellamy William; Powis Garth. (The H. Lee Moffitt Cancer Center & Research Institute, University of South Florida, Tampa, Fl. 33612, USA.. ListAF@Moffitt.usf.edu) . Experimental hematology, (2004 Jun) Vol. 32, No. 6, pp. 526-35. Journal code: 0402313. ISSN: 0301-472X. Pub. country: Netherlands. Language: English.

AB OBJECTIVE: Vascular endothelial growth factor (VEGF) interacts with two high-affinity receptor tyrosine kinases (RTK) on vascular endothelium to initiate complementary but disparate biologic responses. We previously reported that acute myeloid leukemia (AML) cells express VEGF and one or both VEGF-A receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2). To evaluate receptor-selective trophic response to VEGF-A in AML cells, we investigated receptor-specific ligand activation responsible for VEGF-initiated clonogenic response. MATERIALS AND METHODS: Using KG1 (VEGFR-1+/VEGFR-2+) and HL60 (VEGFR-1+) cells with differential VEGF receptor display, we investigated ligand-induced clonogenic response and receptor-initiated signaling after stimulation with VEGF-A, the VEGFR-1 selective ligand placental growth factor (PlGF), or receptor-specific antibody agonists. RESULTS: Recombinant human (rhu)-VEGF increased S-phase fraction and stimulated colony formation in both KG1 and HL60 cells. Ligation of VEGFR-1 or VEGFR-2 with receptor-specific antibody agonists triggered equivalent and concentration-dependent stimulation of colony recovery in KG1 cells, whereas clonogenic response in HL60 cells was restricted to VEGFR-1 activation by antibody or PlGF. In serum-deprived KG1 and HL60 cells, rhu-VEGF stimulated rapid and sustained phosphorylation of Akt/PKB that was inhibited by the phosphatidyl inositol 3-kinase (PI3-K) kinase inhibitor wortmannin. Preincubation with wortmannin inhibited VEGF-induced colony formation in a concentration-dependent fashion. rhu-VEGF-induced clonogenic response and Akt phosphorylation was abolished by the VEGF-RTK inhibitor SU-5416 at concentrations greater than 10 microM, whereas MEK inhibition by PD98059 (1 and 10 microM) was ineffective. In vivo suppression of Akt phosphorylation was confirmed in myeloblast lysates from three patients with advanced myeloid malignancies treated with SU5416. CONCLUSION: These data indicate that VEGF interaction with either VEGFR-1 or VEGFR-2 initiates a clonogenic response in AML cells that is PI3-kinase dependent. RTK inhibitors with broad specificity for angiogenic receptors represent novel therapeutics that merit further clinical investigation in AML.

L21 ANSWER 4 OF 9 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

2002:365178 The Genuine Article (R) Number: 543TN. Vascular endothelial growth factor signaling pathway as an emerging target in hematologic malignancies. List A F (Reprint). Univ Arizona, Arizona Canc Ctr, Rm 3945, 1515 N Campbell Ave, Tucson, AZ 85724 USA (Reprint); Univ Arizona,

Arizona Canc Ctr, Tucson, AZ 85724 USA. ONCOLOGIST (2001) Vol. 6, Supp. [5], pp. 24-31. ISSN: 1083-7159. Publisher: ALPHAMED PRESS, ONE PRESTIGE PLACE, STE 290, MIAMISBURG, OH 45342-3758 USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Angiogenesis is important in a variety of physiologic and pathologic disorders. It is a central element in embryogenesis, ovulation, wound healing, diabetic retinopathy, and rheumatoid arthritis and in the establishment and spread of malignant tumors. Angiogenic factors include direct angiogens, indirect angiogens, and integrins. Direct angiogens stimulate the formation of new blood vessels directly. Indirect angiogens promote neovascular formation by paracrine stimulation of direct angiogens. Integrins mediate interactions between the developing vessels and components of the extracellular matrix. Vascular endothelial growth factor (VEGF) is a principal direct angiogen. By binding to I of 3 receptors (VEGFR-1, -2, or -3), it influences vasculogenesis during embryogenesis, physiologic and neoplastic angiogenesis, and lymphangiogenesis. Although the importance of angiogenesis in solid tumors has been recognized for some time, its exact significance in hematologic malignancies is less clear. Evidence now suggests that VEGF has a major role in the development and progression of hematologic malignancies such as acute leukemia, chronic leukemia, myelodysplasia, non-Hodgkin's lymphoma, and multiple myeloma. Potential therapeutic interventions to interrupt the VEGF signaling pathway of malignancy include antibodies that neutralize the growth factor and small molecules that inhibit the receptor tyrosine kinase activity of VEGF receptors.

L21 ANSWER 5 OF 9 MEDLINE on STN

2000283618. PubMed ID: 10748050. Homeostatic modulation of cell surface KDR and Flt1 expression and expression of the vascular endothelial cell growth factor (VEGF) receptor mRNAs by VEGF. Wang D; Donner D B; Warren R S. (Surgical Oncology Laboratory, Department of Surgery, University of California at San Francisco, San Francisco, California 94143-0790, USA.) The Journal of biological chemistry, (2000 May 26) Vol. 275, No. 21, pp. 15905-11. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Vascular endothelial cell growth factor (VEGF) is a potent angiogenic factor expressed during embryonic development, during wound healing, and in pathologies dependent on neovascularization, including cancer. Regulation of the receptor tyrosine kinases, KDR and Flt-1, to which VEGF binds on endothelial cells is incompletely understood. Chronic incubation with tumor-conditioned medium or VEGF diminished (125)I-VEGF binding to human umbilical vein endothelial cells, incorporation of (125)I-VEGF into covalent complexes with KDR and Flt1, and immunoreactive KDR in cell lysates. Receptor down-regulation desensitized VEGF activation of mitogen-activated protein kinase (extracellular signal-regulated kinases 1 and 2) and p38 mitogen-activated protein kinase. Preincubation with VEGF or tumor-conditioned medium down-regulated cell surface receptor expression but up-regulated KDR and Flt-1 mRNAs, an effect abrogated by a neutralizing VEGF antibody. Removal of VEGF from the medium led to recovery of (125)I-VEGF binding and resensitization of human umbilical vein endothelial cells. Recovery of receptor expression was inhibited by cycloheximide, indicating that augmented VEGF receptor mRNAs, and not receptor recycling from a cytoplasmic pool, restored responsiveness. As the VEGF receptors promote endothelial cell survival, proliferation, and other events necessary for angiogenesis, the noncoordinate regulation of VEGF receptor proteins and mRNAs suggests that human umbilical vein endothelial cells are protected against inappropriate or prolonged loss of VEGF receptors by a homeostatic mechanism important to endothelial cell function.

L21 ANSWER 6 OF 9 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

2000:728769 The Genuine Article (R) Number: 356HQ. Hypoxia-induced VEGF

enhances tumor survivability via suppression of serum deprivation-induced apoptosis. Baek J H; Jang J E; Kang C M; Chung H Y; Kim N D; Kim K W (Reprint). Pusan Natl Univ, Dept Mol Biol, Pusan 609735, South Korea (Reprint); Seoul Natl Univ, WHO, Collaborat Ctr Phys Culture & Aging Res Hlth Prom, Seoul 110799, South Korea; Pusan Natl Univ, Dept Pharm, Pusan 609735, South Korea. ONCOGENE (21 SEP 2000) Vol. 19, No. 40, pp. 4621-4631 . ISSN: 0950-9232. Publisher: NATURE PUBLISHING GROUP, HOUNDMILLS, BASINGSTOKE RG21 6XS, HAMPSHIRE, ENGLAND. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Low oxygen and nutrient depletion play critical roles in tumorigenesis, but little is known about how they interact to produce tumor survival and tumor malignancy. In the present study, we investigated the mechanism underlying hypoxia-modulated apoptosis of serum-deprived HepG2 cells, Our results showed that hypoxia blocked the apoptosis, which was accompanied with decreased Bax/ Bcl-2 ratio, inhibited cytochrome c release, and reduced caspase-3 activity. More importantly, increased expressions of VEGF and its receptor-2 (KDR) under hypoxic/ serum-deprived condition suggest that VEGF may act as a survival factor in a self-promoting manner. Data were further supported by results that recombinant human VEGF (rhVEGF) suppressed the serum deprivation-induced apoptosis, and anti-VEGF neutralizing antibody block anti-apoptotic activity of hypoxia, In addition, inhibitors of receptor tyrosine kinase blocked anti-apoptosis of hypoxia, Our study further showed that rhVEGF or hypoxia induced ERK phosphorylation in serum-deprived cells, and that a specific inhibitor of MAPK/ERK, PD98059 eliminated the anti-apoptotic activity of rhVEGF or hypoxia by increasing Bax/Bcl-2 ratio and caspase-3 activity. Our data led us to conclude that induction of ERK phosphorylation and decrease of Bax/Bcl-2 ratio by rhVEGF implies that hypoxia-induced VEGF prevents apoptosis of serum-deprived cells by activating the MAPK/ERK pathway. Taken together, we propose that hypoxia enhances survival of nutrient-depleted tumor cells by reducing susceptibility to apoptosis, which consequently leads to tumor malignancy.

L21 ANSWER 7 OF 9 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
2001:301433 Document No.: PREV200100301433. VEGFR-1 (Flt-1) and VEGFR-2 (KDR) stimulate the proliferation of AML cells via the PI3-kinase and Akt/protein kinase-B (PKB) signal pathway. List, A. F. [Reprint author]; Glinsmann-Gibson, B. [Reprint author]; Stadheim, C. [Reprint author]; Meuillet, E. [Reprint author]; Bellamy, W. [Reprint author]; Powis, G. [Reprint author]. Arizona Cancer Center, University of Arizona, Tucson, AZ, USA. Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 301a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology. San Francisco, California, USA. December 01-05, 2000. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

AB Vascular endothelial growth factor (VEGF) interacts with two type III receptor tyrosine kinases (RTK) on endothelial cells to initiate separate and distinct biological responses: VEGFR-1 (Flt-1), permeability; and VEGFR-2 (KDR/Flk-1), proliferation. We previously reported that AML cells express VEGF and one or both VEGF receptors (Bellamy et al. Blood (Suppl 1) 1999). Recent reports indicate that VEGF is essential to AML engraftment in SCID mouse models, and that myeloblast VEGF content inversely correlates with treatment outcome. To characterize the biological effects of VEGF in AML, we investigated clonogenic response to rhu-VEGF in receptor competent KG1 (Flt-1+/ KDR+) and HL60 (Flt-1+/KDR-) AML cell lines, and analyzed the roles of phosphoinositide-3-kinase (PI3K), Akt/Protein kinase-B (PKB), and ras mitogen-activated protein kinase kinase (MAPKK/MEK) in receptor signal transduction. Rhu-VEGF (0.1 to 50 ng/ml) stimulated colony formation up to 2.5-fold and increased colony size in each cell line in methylcellulose cultures. To discern receptor specificity of clonogenic response, we assessed colony formation after stimulation with receptor-specific agonist antibodies. 24-hour

exposure to anti-VEGFR-1 or anti-VEGFR-2 triggered equivalent and concentration-dependent stimulation of colony recovery in KG1 cells; whereas clonogenic response in KDR-negative HL60 cells was restricted to Flt-1 engagement. Preincubation with the irreversible PI3K inhibitor wortmannin (1-50nM) inhibited VEGF-induced colony formation in a concentration dependent fashion. In serum deprived KG1 and HL60 cells, rhu-VEGF stimulated rapid (1H) and sustained (24H) phosphorylation of Akt/PKB that was inhibited by wortmannin pre-incubation.Rhu-VEGF-induced clonogenic response and Akt-phosphorylation was abolished by the selective VEGF-RTK inhibitor SU-5416 (Sugen, Inc; San Francisco, CA) at concentrations >10muM; whereas the MAPKK/MEK inhibitor PD98059 (1muM and 10muM) had no effect. These data indicate that VEGF ligation of either VEGFR-1 or VEGFR-2 stimulates a receptor tyrosine kinase-dependent clonogenic response in AML cells that is mediated by PI3-kinase dependent activation of Akt/PBK. VEGF-RTK inhibitors such as SU-5416 represent novel therapeutics that merit clinical investigation in AML.

L21 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN

1999:692135 Document No. 132:704 A role for cadherin-5 in regulation of vascular endothelial growth factor receptor 2 activity in endothelial cells. Rahimi, Nader; Kazlauskas, Andrius (School of Medicine, Boston University, Boston, MA, 02028, USA). Molecular Biology of the Cell, 10(10), 3401-3407 (English) 1999. CODEN: MBCEEV. ISSN: 1059-1524. Publisher: American Society for Cell Biology.

AB FLK-1/vascular endothelial growth factor receptor 2 (VEGFR-2) is one of the receptors for VEGF. In this study we examined the effect of cell d. on activation of VEGFR-2. VEGF induces only very slight tyrosine phosphorylation of VEGFR-2 in confluent (95-100% confluent) pig aortic endothelial (PAE) cells. In contrast, robust VEGF-dependent tyrosine phosphorylation of VEGFR-2 was observed in cells plated in sparse culture conditions (60-65% confluent). A similar cell d.-dependent phenomenon was observed in different endothelial cells but not in NIH-3T3 fibroblast cells expressing VEGFR-2. Stimulating cells with high concns. of VEGF or replacing the extracellular domain of VEGFR-2 with that of the colony-stimulating factor 1 receptor did not alleviate the sensitivity of VEGFR-2 to cell d., indicating that the confluent cells were probably not secreting an antagonist to VEGF. Furthermore, in PAE cells, ectopically introduced platelet-derived growth factor α receptor could be activated at both high and low cell d. conditions, indicating that the d. effect was not universal for all receptor tyrosine kinases expressed in endothelial cells. In addition to lowering the d. of cells, removing divalent cations from the medium of confluent cells potentiated VEGFR-2 phosphorylation in response to VEGF. These findings suggested that cell-cell contact may be playing a role in regulating the activation of VEGFR-2. To this end, pretreatment of confluent PAE cells with a neutralizing anti-cadherin-5 antibody potentiated the response of VEGFR-2 to VEGF. Our data demonstrate that endothelial cell d. plays a critical role in regulating VEGFR-2 activity, and that the underlying mechanism appears to involve cadherin-5.

L21 ANSWER 9 OF 9 MEDLINE on STN

1999438437. PubMed ID: 10506722. KDR activation in astrocytic neoplasms. Carroll R S; Zhang J; Bello L; Melnick M B; Maruyama T; McL Black P. (Neurosurgical Laboratories, Brigham and Women's Hospital, Boston, Massachusetts 02115, USA.) Cancer, (1999 Oct 1) Vol. 86, No. 7, pp. 1335-41. Journal code: 0374236. ISSN: 0008-543X. Pub. country: United States. Language: English.

AB BACKGROUND: The development of new capillary networks appears to be necessary for the growth of solid tumors. Tumor angiogenesis is believed to be mediated by soluble factors released from tumor cells that then act on endothelial cells in a paracrine manner. Vascular endothelial growth factor (VEGF) is a prime regulator of normal and tumor angiogenesis as well as vasculogenesis. VEGF is expressed in glioma cells and its

receptors (Flt-1 and KDR) are expressed in the same gliomas. The two receptors are tyrosine kinases and have an extracellular domain containing seven immunoglobulin-like loops and a split tyrosine-kinase domain. KDR is a receptor for the various VEGF isoforms and for VEGF-C; Flt-1 is a receptor for the various isoforms. Studies suggest that the VEGF receptors are induced in endothelial cells during tumor angiogenesis. Stimulation of aortic endothelial cells results in receptor tyrosine phosphorylation (receptor activation). In this study the activation state of the KDR receptors was determined in low grade, anaplastic, and high grade gliomas. METHODS: A synthetic tyrosine phosphopeptide was used to raise an antibody that recognizes the phosphorylation state of tyrosine 1054/1059 in the KDR receptor. Western blot analysis was performed on 37 astrocytic neoplasms (7 low grade astrocytomas, 13 anaplastic astrocytomas, and 17 cases of glioblastoma multiforme). RESULTS: Immunoblotting with this antibody found that tyrosines 1054/1059 were phosphorylated constitutively within multiple fresh surgical specimens of glioblastomas (71%) and anaplastic gliomas (15%), but not in low grade gliomas. CONCLUSIONS: The findings of the current study strongly support the hypothesis that the onset of angiogenesis is an important event during the disease progression of gliomas.

=> s l14 and tyrosine phosphorylation
L22 38 L14 AND TYROSINE PHOSPHORYLATION

=> dup remove l22
PROCESSING COMPLETED FOR L22
L23 14 DUP REMOVE L22 (24 DUPLICATES REMOVED)

=> d l23 1-14 cbib abs

L23 ANSWER 1 OF 14 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
2006:499055 Document No.: PREV200600505375. Role of MAPK in activation of signal transducers and activators of transcription (STATs) proteins in VEGF stimulated human intestinal microvascular endothelial cells (HIMEC). Rafiee, Parvaneh; Theriot, Monica; Otterson, Mary E.; Binion, David G.. Gastroenterology, (APR 2006) Vol. 130, No. 4, Suppl. 2, pp. A686-A687. Meeting Info.: Digestive Disease Week Meeting/107th Annual Meeting of the American-Gastroenterological-Association. Los Angeles, CA, USA. May 19 -24, 2006. Amer Gastroenterol Assoc Inst.
CODEN: GASTAB. ISSN: 0016-5085. Language: English.
AB INTRODUCTION: VEGF effects on endothelial cells, preventing apoptosis as well as inducing migration, growth, proliferation and differentiation. VEGF activates various signaling cascades (i.e. MAPKs, PI3K/Akt) in HIMEC. STAT proteins modulate cell growth responses, and play a role in endothelial proliferation, but have not been characterized in human intestinal microvascular angiogenesis. We investigated the contribution of STATs signaling pathway in tissues from control and IBD pts as well as control and disease specific HIMEC following VEGF activation. METHODS: Mucosa. from control and IBD (UC and Crohn's disease(CD)) pts were homogenized in hypotonic buffer and nuclear proteins were prepared. Control and IBD HIMEC monolayers were treated with VEGF, and nuclear translocation of STAT proteins was detected by immunofluorescence staining. An ELISA-based oligonucleotide binding assay containing an immobilized STAT consensus binding site was used to demonstrate the DNA binding in nuclear protein extracts. Phospho-STAT proteins were detected by Western bloting using specific phospho-antibodies. Inhibitors of p38 MAPK and p44/42 MAPK were used to identify the signaling pathways. The specific VEGFR2 antibody was used to determine whether STATs activation in HIMEC were mediated through VEGFR2/ KDR receptor. RESULTS: Western bloting revealed phosphorylated STAT1 and STAT3 in both UC and CD intestinal tissues but not the control

and uninvolved mucosal specimens. Similarly DNA-nuclear proteins assay demonstrated increased level of STAT1 and STAT3 but not STAT5A and 5B. VEGF induced tyrosine phosphorylation and nuclear translocation of STAT1 alpha, STAT3, STAT5A and STAT5B in HIMEC. VEGF activated IBD HIMEC (n=4) demonstrated enhanced STAT1 and STAT3 compared with control HIMEC (n=3). Pretreatment of HIMEC with VEGFR2 antibody suppressed STATs phosphorylation and nuclear translocation. The p38 MAPK inhibitor SB203580 decreased STAT1 alpha activation, whereas PD098059 (MEK/p44/42 MAPK inhibitor) suppressed both STAT1 alpha and STAT3 in HIMEC. CONCLUSIONS: Differential STAT activation characterizes intestinal inflammation in IBD tissues and HIMEC.VFGF activates STATs in HIMEC through the VEGFR2/KDR receptor. MAPK family members play a differential role in STATs activation. These findings suggest a role for the STATs in the regulation of gene expression associated with chronic inflammation and the angiogenic effects of VEGF in gut specific microvascular endothelial cells.

L23 ANSWER 2 OF 14 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

2006:209847 Document No.: PREV200600211576. Vascular endothelial growth factor (VEGF) activates signal transducers and activators of transcription (STATs) proteins in human intestinal microvascular endothelial cells (HIMEC). Rafiee, Parvaneh; Theriot, Monica E.; Otterson, Mary F.; Binion, David G.. Gastroenterology, (APR 2005) Vol. 128, No. 4, Suppl. 2, pp. A516.

Meeting Info.: Annual Meeting of the American-Gastroenterological-Association/Digestive-Disease-Week. Chicago, IL, USA. May 14 -19, 2005. Amer Gastroenterol Assoc.

CODEN: GASTAB. ISSN: 0016-5085. Language: English.

AB INTRODUCTION: The angiogenic effect of VEGF is initiated by binding of the tyrosine kinase receptors, VEGFR1/Flt-1 and VEGFR2/Flk-1/KDR expressed on endothelial cells. Following receptor binding, VEGF activates various signaling cascades, including the mitogen activated protein kinase family (MAPKs) and PI3K/Akt, leading to cell cycle re-entry and proliferation of endothelial cells, including human gut specific microvascular endothetial cells (HIMEC). STAT proteins are important modulators of cell growth responses, and have recently been recognized to play a role in endothelial proliferation, but have not been characterized in human intestinal angiogenesis. We investigated the potential contribution of STATs signaling pathways activated by VEGF in HIMEC.METHODS: HIMEC monolayers were treated with VEGF, and nuclear translocation of STAT proteins was detected in nuclear protein extracts by an ELISA-based oligonucleotide binding assay containing an immobilized STAT consensus binding site. By using antibodies against STAT1a, STAT3, STAT5A and STAT5B the STAT complex bound to oligonuleotide was detected. Addition of a secondary antibody conjugated to horseradish peroxidase resulted in a colorimetric readout that was quantified by spectrophotometer. The specific VEGFR2 blocking antibody was used to determine whether STATs activation were mediated through the VEGFR2/KDR receptor.RESULTS: VEGF induced tyrosine phosphorylation arid nuclear translocation of STAT1a, STAT3, STAT5A and SLAT 5B in HIMEC. Pre-treatment of HIMEC with VEGFR2 blocking antibody suppressed STATs phosphorylation and nuclear translocation. The p38 MAPK inhibitor SB203580 decreased STAT1a activation, whereas PD098059 (MEK/p44/42 MAPK inhibitor) suppressed both STAT1a and STAT3 in HIMEC. The tyorsine kinase inhibitor genistein blocked all STATs activation following VEGF stimulation of HIMEC.CONCLUSIONS: VEGF activates STATs pathways through VEGFR2/KDR receptor in HIMEC. The growth promoting activity of VEGF depends upon VEGFR2 activation in HIMEC. These findings suggest a role for the STATs in the regulation of gene expression associated with the angiogenic effects of VEGF in gut specific microvascular endothelial cells.

L23 ANSWER 3 OF 14 MEDLINE on STN DUPLICATE 1

2003431778. PubMed ID: 12844492. Vascular endothelial growth factor regulates focal adhesion assembly in human brain microvascular endothelial cells through activation of the focal adhesion kinase and related adhesion focal tyrosine kinase. Avraham Hava Karsenty; Lee Tae-Hee; Koh Youngho; Kim Tae-Aug; Jiang Shuxian; Sussman Mark; Samarel Allen M; Avraham Shalom. (Division of Experimental Medicine and Hematology/Oncology, Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts 02115, USA.. savraham@bidmc.harvard.edu) . The Journal of biological chemistry, (2003 Sep 19) Vol. 278, No. 38, pp. 36661-8. Electronic Publication: 2003-07-03. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Vascular endothelial growth factor (VEGF) plays a significant role in blood-brain barrier breakdown and angiogenesis after brain injury. VEGF-induced endothelial cell migration is a key step in the angiogenic response and is mediated by an accelerated rate of focal adhesion complex assembly and disassembly. In this study, we identified the signaling mechanisms by which VEGF regulates human brain microvascular endothelial cell (HBMEC) integrity and assembly of focal adhesions, complexes comprised of scaffolding and signaling proteins organized by adhesion to the extracellular matrix. We found that VEGF treatment of HBMECs plated on laminin or fibronectin stimulated cytoskeletal organization and increased focal adhesion sites. Pretreating cells with VEGF antibodies or with the specific inhibitor SU-1498, which inhibits Flk-1/KDR receptor phosphorylation, blocked the ability of VEGF to stimulate focal adhesion assembly. VEGF induced the coupling of focal adhesion kinase (FAK) to integrin alphavbeta5 and tyrosine phosphorylation of the cytoskeletal components paxillin and p130cas. Additionally, FAK and related adhesion focal tyrosine kinase (RAFTK)/Pyk2 kinases were tyrosine-phosphorylated by VEGF and found to be important for focal adhesion sites. Overexpression of wild type RAFTK/Pyk2 increased cell spreading and the migration of HBMECs, whereas overexpression of catalytically inactive mutant RAFTK/Pyk2 markedly suppressed HBMEC spreading (approximately 70%), adhesion (approximately 82%), and migration (approximately 65%). Furthermore, blocking of FAK by the dominant-interfering mutant FRNK (FAK-related non-kinase) significantly inhibited HBMEC spreading and migration and also disrupted focal adhesions. Thus, these studies define a mechanism for the regulatory role of VEGF in focal adhesion complex assembly in HBMECs via activation of FAK and RAFTK/Pyk2.

L23 ANSWER 4 OF 14 MEDLINE on STN DUPLICATE 2

2002455601. PubMed ID: 12214271. Sck is expressed in endothelial cells and participates in vascular endothelial growth factor-induced signaling. Ratcliffe Kirsty E; Tao Qi; Yavuz Burju; Stoletov Konstantin V; Spring Simone C; Terman Bruce I. (Department of Medicine, Cardiology Division, Albert Einstein College of Medicine, Bronx, New York, NY 10461, USA.) Oncogene, (2002 Sep 12) Vol. 21, No. 41, pp. 6307-16. Journal code: 8711562. ISSN: 0950-9232. Pub. country: England: United Kingdom. Language: English.

AB Sck, a member of the Shc family of cell signaling proteins, has only been studied in neuronal cells, though previous studies have demonstrated its expression in tissues other than brain. Using RT-PCR and RNase protection assays, we detected Sck mRNA expression in endothelial cells, and Sck protein was detected by Western blotting using polyclonal and monoclonal antibodies targeting the Sck CH1 domain. Immunohistochemistry protocols demonstrate that Sck is expressed in KDR and PECAM positive cells found in the mouse retina, mouse heart and human umbilical chord. Treatment of human umbilical vein endothelial (HUVE) cells with vascular endothelial growth factor (VEGF) leads to the recruitment of Sck to the KDR VEGF receptor and an enhanced Sck tyrosine phosphorylation. Sck is recruited to KDR tyrosine 1175, as co-immunoprecipitation of KDR and Sck is not observed in VEGF-treated porcine aortic endothelial cells expressing a receptor mutated at this autophosphorylation site. The Sck

and Shc SH2 domains, and not the PTB domain, mediates its interactions with KDR, as recombinant Sck SH2 domain binds to a tyrosine phosphorylated KDR 1175-derived synthetic peptide, but not to a peptide synthesized without tyrosine phosphate. Recombinant PLCgamma SH2 domain also interacts with the phosphotyrosine 1175 containing peptide. VEGF-induced MAPK activation is dependent upon PLCgamma activity, and chimeric proteins consisting of the Shc or Sck SH2 domains fused with a cellular internalization sequence attenuated this activation. Taken together, these results demonstrate that Sck is expressed in vascular endothelial cells, and participates in VEGF-induced signal transduction.

L23 ANSWER 5 OF 14 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

2000:537281 The Genuine Article (R) Number: 332QG. Vascular endothelial growth factor up-regulates ICAM-1 expression via the phosphatidylinositol 3 OH-kinase/AKT/nitric oxide pathway and modulates migration of brain microvascular endothelial cells. Radisavljevic Z; Avraham H; Avraham S (Reprint). Harvard Univ, Sch Med, Inst Med, Beth Israel Deaconess Med Ctr, Dept Med, Div Expt Med, 4 Blackfan Circle, Boston, MA 02115 USA (Reprint); Harvard Univ, Sch Med, Inst Med, Beth Israel Deaconess Med Ctr, Dept Med, Div Expt Med, Boston, MA 02115 USA. JOURNAL OF BIOLOGICAL CHEMISTRY (7 JUL 2000) Vol. 275, No. 27, pp. 20770-20774. ISSN: 0021-9258. Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Endothelium of the cerebral blood microvessels, which constitutes the major component of the blood-brain barrier, controls leukocyte and metastatic cancer cell adhesion and trafficking into the brain parenchyma. In this study, using rat primary brain microvascular endothelial cells (BMEC), we demonstrate that the vascular endothelial growth factor (VEGF), a potent promoter of angiogenesis, up-regulates the expression of the intracellular adhesion molecule-1 (ICAM-1) through a novel pathway that includes phosphatidylinositol 3 OH-kinase (PI3K), AKT, and nitric oxide (NO), resulting in the migration of BMEC. Upon VEGF treatment, AKT is phosphorylated in a PI3K-dependent manner. AKT activation leads to NO production and release and activation-deficient AKT attenuates NO production stimulated by VEGF. Transfection of the constitutive myr-AKT construct significantly increased basal NO release in BMEC. In these cells, VEGF and the endothelium-derived NO synergistically up-regulated the expression of ICAM-1, which was mediated by the PI3K pathway. This activity was blocked by the PI3K-specific inhibitor, wortmannin, Furthermore, VEGF and NO significantly increased BmEC migration, which was mediated by the up-regulation of ICAM-1 expression and was dependent on the integrity of the PI3K/AKT/NO pathway. This effect was abolished by wortmannin, by the specific ICAM-1 antibody, by the specific inhibitor of NO synthase, N-G-L-monomethyl-arginine (L-NMMA) or by a combination of wortmannin, ICAM-1 antibody, and L-NMMA. These findings demonstrate that the angiogenic factor VEGF up-regulates ICAM-1 expression and signals to ICAM-1 as an effector molecule through the PI3K/AKT/NO pathway, which leads to brain microvessel endothelial cell, migration. These observations may contribute to a better understanding of BMEC angiogenesis and the physiological as well as pathophysiological function of the blood-brain barrier, whose integrity is crucial for normal brain function.

L23 ANSWER 6 OF 14 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN DUPLICATE 3

2000:292968 The Genuine Article (R) Number: 302BT. Vascular endothelial growth factor (VEGF)-driven actin-based motility is mediated by VEGFR2 and requires concerted activation of stress-activated protein kinase 2 (SAPK2/p38) and geldanamycin-sensitive phosphorylation of focal adhesion kinase. Rousseau S; Houle F; Kotanides H; Witte L; Waltenberger J; Landry J; Huot J (Reprint). Univ Laval, Hotel Dieu Quebec, Ctr Rech Cancerol, 11 Cote Palais, Quebec City, PQ G1R 2J6, Canada (Reprint); Univ Laval, Hotel

Dieu Quebec, Ctr Rech Cancerol, Quebec City, PQ G1R 2J6, Canada; Univ Ulm, Med Ctr, Dept Internal Med 2, D-89081 Ulm, Germany; ImClone Syst Inc, Dept Mol & Cell Biol, New York, NY 10014 USA. JOURNAL OF BIOLOGICAL CHEMISTRY (7 APR 2000) Vol. 275, No. 14, pp. 10661-10672. ISSN: 0021-9258. Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB In endothelial cells, vascular endothelial growth factor (VEGF) induces an accumulation of stress fibers associated with new actin polymerization and rapid formation of focal adhesions at the ventral surface of the cells. This cytoskeletal reorganization results in an intense motogenic activity. Using porcine endothelial cells expressing one or the other type of the VEGF receptors, VEGFR1 or VEGFR2, or human umbilical vein endothelial cells pretreated with a VEGFR2 neutralizing antibody, we show that VEGFR2 is responsible for VEGF-induced activation of the stress-activated protein kinase-2/p38 (SAPK2/p38), phosphorylation of focal adhesion kinase (FAK), and enhanced migratory activity. Activation of SAPK2/p38 triggered actin polymerization whereas FAX, which was phosphorylated independently of SAPK2/p38, initiated assembly of focal adhesions. Both processes contributed to the formation of stress fibers. Geldanamycin, an inhibitor of HSP90 blocked tyrosine phosphorylation of FAK, assembly of focal adhesions, actin reorganization, and cell, migration, all of which were reversed by overexpressing HSP90. We conclude that VEGFR2 mediates the physiological effect of VEGF on cell migration and that two independent pathways downstream of VEGFR2 regulate actin-based motility. One pathway involves SAPK2/p38 and leads to enhanced actin polymerization activity. The other involves HSP90 as a permissive signal transduction factor implicated in FAK phosphorylation and assembly of focal adhesions.

L23 ANSWER 7 OF 14 MEDLINE on STN

2001077245. PubMed ID: 11118060. HGF/NK4, a four-kringle antagonist of hepatocyte growth factor, is an angiogenesis inhibitor that suppresses tumor growth and metastasis in mice. Kuba K; Matsumoto K; Date K; Shimura H; Tanaka M; Nakamura T. (Department of Oncology, Biomedical Research Center, Osaka University Medical School, Suita, Japan.) Cancer research, (2000 Dec 1) Vol. 60, No. 23, pp. 6737-43. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB We reported that NK4, composed of the N-terminal hairpin and subsequent four kringle domains of hepatocyte growth factor (HGF), acts as the competitive antagonist for HGF. We now provide the first evidence that NK4 inhibits tumor growth and metastasis as an angiogenesis inhibitor as well as an HGF antagonist. Administration of NK4 suppressed primary tumor growth and lung metastasis of Lewis lung carcinoma and Jyg-MC(A) mammary carcinoma s.c. implanted into mice, although neither HGF nor NK4 affected proliferation and survival of these tumor cells in vitro. NK4 treatment resulted in a remarkable decrease in microvessel density and an increase of apoptotic tumor cells in primary tumors, which suggests that the inhibition of primary tumor growth by NK4 may be achieved by suppression of tumor angiogenesis. In vivo, NK4 inhibited angiogenesis in chick chorioallantoic membranes and in rabbit corneal neovascularization induced by basic fibroblast growth factor (bFGF). In vitro, NK4 inhibited growth and migration of human microvascular endothelial cells induced by bFGF and vascular endothelial growth factor (VEGF) as well as by HGF. HGF and VEGF activated the Met/HGF receptor and the KDR/VEGF receptor, respectively, whereas NK4 inhibited HGF-induced Met tyrosine phosphorylation but not VEGF-induced KDR phosphorylation. NK4 inhibited HGF-induced ERK1/2 (p44/42 mitogen-activated protein kinase) activation, but allowed for bFGF- and VEGF-induced ERK1/2 activation. These results indicate that NK4 is an angiogenesis inhibitor as well as an HGF antagonist, and that the antiangiogenic action of NK4 is independent of its activity as HGF antagonist. The bifunctional properties of NK4 to act as an angiogenesis inhibitor and as an HGF antagonist raises the

possibility that NK4 may prove therapeutic for cancer patients.

L23 ANSWER 8 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
1999:692135 Document No. 132:704 A role for cadherin-5 in regulation of vascular endothelial growth factor receptor 2 activity in endothelial cells. Rahimi, Nader; Kazlauskas, Andrius (School of Medicine, Boston University, Boston, MA, 02028, USA). Molecular Biology of the Cell, 10(10), 3401-3407 (English) 1999. CODEN: MBCEEV. ISSN: 1059-1524. Publisher: American Society for Cell Biology.
AB FLK-1/vascular endothelial growth factor receptor 2 (VEGFR-2) is one of the receptors for VEGF. In this study we examined the effect of cell d. on activation of VEGFR-2. VEGF induces only very slight tyrosine phosphorylation of VEGFR-2 in confluent (95-100% confluent) pig aortic endothelial (PAE) cells. In contrast, robust VEGF-dependent tyrosine phosphorylation of VEGFR-2 was observed in cells plated in sparse culture conditions (60-65% confluent). A similar cell d.-dependent phenomenon was observed in different endothelial cells but not in NIH-3T3 fibroblast cells expressing VEGFR-2. Stimulating cells with high concns. of VEGF or replacing the extracellular domain of VEGFR-2 with that of the colony-stimulating factor 1 receptor did not alleviate the sensitivity of VEGFR-2 to cell d., indicating that the confluent cells were probably not secreting an antagonist to VEGF. Furthermore, in PAE cells, ectopically introduced platelet-derived growth factor α receptor could be activated at both high and low cell d. conditions, indicating that the d. effect was not universal for all receptor tyrosine kinases expressed in endothelial cells. In addition to lowering the d. of cells, removing divalent cations from the medium of confluent cells potentiated VEGFR-2 phosphorylation in response to VEGF. These findings suggested that cell-cell contact may be playing a role in regulating the activation of VEGFR-2. To this end, pretreatment of confluent PAE cells with a neutralizing anti-cadherin-5 antibody potentiated the response of VEGFR-2 to VEGF. Our data demonstrate that endothelial cell d. plays a critical role in regulating VEGFR-2 activity, and that the underlying mechanism appears to involve cadherin-5.

L23 ANSWER 9 OF 14 MEDLINE on STN DUPLICATE 4
1999438437. PubMed ID: 10506722. KDR activation in astrocytic neoplasms. Carroll R S; Zhang J; Bello L; Melnick M B; Maruyama T; McL Black P. (Neurosurgical Laboratories, Brigham and Women's Hospital, Boston, Massachusetts 02115, USA.) Cancer, (1999 Oct 1) Vol. 86, No. 7, pp. 1335-41. Journal code: 0374236. ISSN: 0008-543X. Pub. country: United States. Language: English.
AB BACKGROUND: The development of new capillary networks appears to be necessary for the growth of solid tumors. Tumor angiogenesis is believed to be mediated by soluble factors released from tumor cells that then act on endothelial cells in a paracrine manner. Vascular endothelial growth factor (VEGF) is a prime regulator of normal and tumor angiogenesis as well as vasculogenesis. VEGF is expressed in glioma cells and its receptors (Flt-1 and KDR) are expressed in the same gliomas. The two receptors are tyrosine kinases and have an extracellular domain containing seven immunoglobulin-like loops and a split tyrosine-kinase domain. KDR is a receptor for the various VEGF isoforms and for VEGF-C; Flt-1 is a receptor for the various isoforms. Studies suggest that the VEGF receptors are induced in endothelial cells during tumor angiogenesis. Stimulation of aortic endothelial cells results in receptor tyrosine phosphorylation (receptor activation). In this study the activation state of the KDR receptors was determined in low grade, anaplastic, and high grade gliomas. METHODS: A synthetic tyrosine phosphopeptide was used to raise an antibody that recognizes the phosphorylation state of tyrosine 1054/1059 in the KDR receptor. Western blot analysis was performed on 37 astrocytic neoplasms (7 low grade astrocytomas, 13 anaplastic astrocytomas, and 17 cases of glioblastoma

multiforme). RESULTS: Immunoblotting with this antibody found that tyrosines 1054/1059 were phosphorylated constitutively within multiple fresh surgical specimens of glioblastomas (71%) and anaplastic gliomas (15%), but not in low grade gliomas. CONCLUSIONS: The findings of the current study strongly support the hypothesis that the onset of angiogenesis is an important event during the disease progression of gliomas.

L23 ANSWER 10 OF 14 MEDLINE on STN DUPLICATE 5
1999137695. PubMed ID: 9950855. Role of phospholipase C, protein kinase C, and calcium in VEGF-induced venular hyperpermeability. Wu H M; Yuan Y; Zawieja D C; Tinsley J; Granger H J. (Departments of Medical Physiology and Surgery, Texas A & M University System Health Science Center, Temple, Texas 76504, USA.) The American journal of physiology, (1999 Feb) Vol. 276, No. 2 Pt 2, pp. H535-42. Journal code: 0370511. ISSN: 0002-9513. Pub. country: United States. Language: English.
AB We previously demonstrated that vascular endothelial growth factor (VEGF)-elicited increase in the permeability of coronary venules was blocked by the nitric oxide (NO) synthase inhibitor NG-monomethyl-L-arginine (L-NMMA). The aim of this study was to delineate in more detail the signaling pathways upstream from NO production in VEGF-induced venular hyperpermeability. The apparent permeability coefficient of albumin (Pa) and endothelial cytosolic Ca2+ concentration ([Ca2+]i) were measured in intact perfused porcine coronary venules using fluorescence microscopy. VEGF (10(-10) M) induced a two- to threefold increase in Pa, which was blocked by a monoclonal antibody directed against the VEGF receptor Flk-1/KDR, the phospholipase C (PLC) antagonist U-73122, or the protein kinase C (PKC) antagonist bisindolylmaleimide (BIM). In 12 venules that displayed the [Ca2+]i response to bradykinin (10(-6) M) and ionomycin (10(-6) M), only 4 vessels responded to VEGF with a transient increase in [Ca2+]i. Furthermore, Western blot analysis of cultured human umbilical vein endothelial cells showed that VEGF increased tyrosine phosphorylation of PLC-gamma and serine phosphorylation of endothelial constitutive NO synthase (ecNOS). The hyperphosphorylation of PLC-gamma was greatly attenuated by the KDR receptor antibody and U-73122, but not by BIM or L-NMMA. In contrast, U-73122 and BIM were able to inhibit VEGF-elicited serine phosphorylation of ecNOS. The results suggest that VEGF induces venular hyperpermeability through a KDR receptor-mediated activation of PLC. In turn, ecNOS is activated by PLC-mediated PKC and/or cytosolic Ca2+ elevation stimulation.

L23 ANSWER 11 OF 14 EMBASE
1999078512 EMBASE Role of phospholipase C, protein kinase C, and calcium in VEGF-induced venular hyperpermeability. Wu H.M.; Yuan Y.; Zawieja D.C.; Tinsley J.; Granger H.J.. H.M. Wu, Dept. of Medical Physiology, Texas A and M Univ. Hlth. Sci. Ctr., Bldg. 4, 1901 South First St., Temple, TX 76504, United States. American Journal of Physiology - Heart and Circulatory Physiology Vol. 276, No. 2 45-2, pp. H535-H542 1999.
Refs: 34.
ISSN: 0363-6135. CODEN: AJPPDI
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 19990326. Last Updated on STN: 19990326
AB We previously demonstrated that vascular endothelial growth factor (VEGF)-elicited increase in the permeability of coronary venules was blocked by the nitric oxide (NO) synthase inhibitor N(G)-monomethyl-L-arginine (L- NMMA). The aim of this study was to delineate in more detail the signaling pathways upstream from NO production in VEGF-induced venular hyperpermeability. The apparent permeability coefficient of albumin (P(a)) and endothelial cytosolic Ca2+ concentration ([Ca2+](i)) were measured in intact perfused porcine coronary venules using fluorescence microscopy. VEGF (10-10 M) induced a two- to threefold increase in P(a), which was blocked by a monoclonal antibody directed against the

VEGF receptor Flk-1/KDR, the phospholipase C (PLC) antagonist U-73122, or the protein kinase C (PKC) antagonist bisindolylmaleimide (BIM). In 12 venules that displayed the [Ca2+](i) response to bradykinin (10-6 M) and ionomycin (10-6 M), only 4 vessels responded to VEGF with a transient increase in [Ca2+](i). Furthermore, Western blot analysis of cultured human umbilical vein endothelial cells showed that VEGF increased tyrosine phosphorylation of PLC- γ and serine phosphorylation of endothelial constitutive NO synthase (ecNOS). The hyperphosphorylation of PLC-γ was greatly attenuated by the KDR receptor antibody and U-73122, but not by BIM or L-NMMA. In contrast, U- 73122 and BIM were able to inhibit VEGF-elicited serine phosphorylation of ecNOS. The results suggest that VEGF induces venular hyperpermeability through a KDR receptor-mediated activation of PLC. In turn, ecNOS is activated by PLC-mediated PKC and/or cytosolic Ca2+ elevation stimulation.

L23 ANSWER 12 OF 14 MEDLINE on STN DUPLICATE 6

1998311244. PubMed ID: 9648910. Virally activated Ras cooperates with integrin to induce tubulogenesis in sinusoidal endothelial cell lines. Maru Y; Yamaguchi S; Takahashi T; Ueno H; Shibuya M. (Department of Genetics, Institute of Medical Science, University of Tokyo, Japan.. ymaru@hgc.ims.u-tokyo.ac.jp) . Journal of cellular physiology, (1998 Aug) Vol. 176, No. 2, pp. 223-34. Journal code: 0050222. ISSN: 0021-9541. Pub. country: United States. Language: English.

AB Four cell lines, named nonparenchymal 11 (NP11), NP26, NP31, and NP32, were established from sinusoidal endothelial cells (SECs) of rat liver. They still retained expression of receptors for vascular endothelial growth factor (VEGF), Fit-1, and kinase domain-containing receptor (KDR). NP31 and NP32 turned out to be incapable of tubulogenesis in basement membrane matrix (Matrigel), which belongs to endothelial properties, as shown by SECs in primary culture. Expression of temperature-sensitive, virally activated Ras (ts-v-Ras) restored tubulogenic behaviors back to NP31 only at permissive temperature. Matrigel induced long-lasting tyrosine phosphorylation of Shc, with recruitment of Grb-2 and microtubule-associated protein kinase (MAPK) activation in both parental NP31 and NP31 transformed by ts-v-Ras, which was blocked by anti-beta1 integrin antibody. Tubulogenesis was inhibited by adenovirus-mediated expression of dominant-negative Ras in human umbilical vein endothelial cells (HUVECs). PD 098059, a selective inhibitor of MAPK kinase (MEK), nearly perfectly blocked tubulogenesis by ts-v-Ras-expressing NP31 cells at permissive temperature. Furthermore, the botulinum C3 toxin, an inhibitor for Rho, caused fragmentation of branching cords in networks formed by NP31 that expressed ts-v-Ras at permissive temperature. These data suggest that the integrin-mediated Ras signals may be necessary but are not sufficient for tubulogenesis and that an artificial expression of v-Ras might substitute for the second signal required in this system.

L23 ANSWER 13 OF 14 MEDLINE on STN

97326125. PubMed ID: 9182576. Vascular endothelial growth factor stimulates tyrosine phosphorylation and recruitment to new focal adhesions of focal adhesion kinase and paxillin in endothelial cells. Abedi H; Zachary I. (Cruciform Project and Department of Medicine, University College London, 5 University Street, London WC1E 6JJ, United Kingdom.) The Journal of biological chemistry, (1997 Jun 13) Vol. 272, No. 24, pp. 15442-51. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Vascular endothelial growth factor (VEGF) stimulated the tyrosine phosphorylation of multiple components in confluent human umbilical vein endothelial cells (HUVECs) including bands of Mr 205,000, corresponding to the VEGF receptors Flt-1 and KDR, and Mr 145,000, 120,000, 97,000, and 65,000-70,000. VEGF caused a striking and transient increase in mitogen-activated protein (MAP) kinase activity and stimulated phospholipase C-gamma tyrosine phosphorylation, but it had no effect on phosphatidylinositol

3'-kinase activity. VEGF caused a marked increase in tyrosine phosphorylation of p125 focal adhesion kinase (p125(FAK)), which was both rapid and concentration-dependent. VEGF produced similar effects on p125(FAK) in the endothelial cell line ECV.304. VEGF stimulated tyrosine phosphorylation of the 68-kDa focal adhesion-associated component, paxillin, with similar kinetics and concentration dependence to that for p125(FAK). Thrombin and the phorbol ester, phorbol 12-myristate 13-acetate, also increased p125(FAK) tyrosine phosphorylation in HUVECs. The effect of VEGF on p125(FAK) tyrosine phosphorylation was completely inhibited by the actin filament-disrupting agent cytochalasin D and was partially inhibited by the protein kinase C inhibitor GF109203X. Inhibition of the MAP kinase pathway using a specific inhibitor of MAP kinase kinase had no effect on p125(FAK) tyrosine phosphorylation. VEGF stimulated migration and actin stress fiber formation in confluent HUVEC, and VEGF-induced p125(FAK)/paxillin tyrosine phosphorylation was accompanied by increased immunofluorescent staining of p125(FAK), paxillin, and phosphotyrosine in focal adhesions in confluent cultures of HUVECs. These findings identify p125(FAK) and paxillin as components in a VEGF-stimulated signaling pathway and suggest a novel mechanism for VEGF regulation of endothelial cell functions.

L23 ANSWER 14 OF 14 MEDLINE on STN DUPLICATE 7

97338294. PubMed ID: 9194854. Role of VEGF receptor-1 (Flt-1) in mediating calcium-dependent nitric oxide release and limiting DNA synthesis in human trophoblast cells. Ahmed A; Dunk C; Kniss D; Wilkes M. (Department of Obstetrics and Gynaecology, Birmingham Women's Hospital, Edgbaston, United Kingdom.) Laboratory investigation; a journal of technical methods and pathology, (1997 Jun) Vol. 76, No. 6, pp. 779-91. Journal code: 0376617. ISSN: 0023-6837. Pub. country: United States. Language: English.

AB Vascular endothelial growth factor (VEGF) receptor KDR (kinase-insert-domain-containing receptor) is linked to endothelial cell proliferation, and VEGF receptor Flt-1 (fms-like tyrosine kinase) is essential for the organization of embryonic vasculature. Flt-1 is also known to be expressed on adult endothelial and trophoblast cells, although its function has not yet been established. Herein we report that human trophoblast and endothelial cells contain functional Flt-1 receptors for VEGF that trigger the synthesis and release of nitric oxide (NO) by the activation of constitutive NO synthase (cNOS). In first-trimester human trophoblast cells isolated by chorionic villous sampling, VEGF165 stimulated NO release in a concentration- and time-dependent manner, with a maximal increase of 60% (in comparison to basal release levels) occurring within 30 minutes (basal: 1342 pmol/ml; VEGF (10 ng/ml): 2162 pmol/ml; $p < 0.001$), as measured by an NO chemiluminescence analyzer. VEGF20, a peptide fragment that is composed of the first 20 amino acids at N-terminus, displayed properties of a partial agonist. VEGF165- and VEGF20-mediated NO biosynthesis was attenuated by NG-nitro-L-arginine in a concentration-dependent fashion, indicating NOS activation. VEGF-neutralizing anti-VEGF monoclonal antibody significantly inhibited VEGF-mediated NO release ($p < 0.001$), and the addition of a neutralizing anti-Flt-1 antibody inhibited the response by 79.6% +/- 7.59%, an effect found to be reversible with higher concentrations of VEGF. In contrast, anti-KDR antibody had no significant inhibitory effect. RT-PCR confirmed the presence of mRNA encoding the Flt-1 and KDR receptors as well as the endothelial form of cNOS in trophoblast cells. VEGF165-stimulated NO release was inhibited by genistein (5 microM; $p < 0.001$) as well as by the removal of calcium from the extracellular environment ($p < 0.001$), which suggests the contingency of this process on tyrosine phosphorylation and extracellular calcium, respectively. Addition of sodium nitroprusside, an NO donor, inhibited trophoblast DNA synthesis in a concentration-dependent manner, as measured by [3H]thymidine incorporation, without affecting cell viability. VEGF under maximal NO production had no mitogenic activity,

suggesting that trophoblast-derived NO may limit trophoblast proliferation. Endogenous trophoblast DNA synthesis increased 3-fold in the presence of anti-Flt-1 antibody but not in the presence of anti-KDR antibody, suggesting that Flt-1 functions as a growth suppressive receptor to counteract the proliferative actions of KDR. Levels of immunoreactive endothelial cNOS were markedly increased in growth-restricted placentae (n = 4) in comparison to those of normal (n = 5) placentae, which may account for the relatively small-sized placentae associated with intrauterine growth restriction. VEGF165 stimulated NO release via phosphorylation of the Flt-1 receptor, indicating that VEGF may be an autocrine regulator of NO biosynthesis by aiding trophoblast penetration into spinal arterioles during the first trimester and preventing platelet aggregation within the placenta. Finally, the activation of Flt-1 receptor suppressed trophoblast DNA synthesis within the placenta via NO.

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=> d his

     (FILE 'HOME' ENTERED AT 10:58:11 ON 15 NOV 2006)

     FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 10:58:36 ON
     15 NOV 2006
L1        971735 S PROBE
L2           145 S L1 AND KDR
L3            16 S L2 AND ACTIVATION
L4             8 DUP REMOVE L3 (8 DUPLICATES REMOVED)
L5            17 S L2 AND PHOSPHORYLATION
L6             9 DUP REMOVE L5 (8 DUPLICATES REMOVED)
L7            67 S L1 AND FLK-1
L8             9 S L7 AND ACTIVATION
L9             3 S L7 AND PHOSPHORYLATION
L10            3 DUP REMOVE L9 (0 DUPLICATES REMOVED)
L11      2882174 S ANTIBOD?
L12         1368 S L11 AND KDR
L13          596 S L12 AND TYROSINE
L14          170 S L13 AND ACTIVATION
L15            0 S L14 AND 1215
L16            1 S L14 AND 1214
L17            0 S L14 AND CDPKFHYDNTAGIS
L18            0 S L14 AND CDPKFHYDNTAGIS
L19           74 DUP REMOVE L14 (96 DUPLICATES REMOVED)
L20            9 S L19 AND RECEPTOR TYROSINE
L21            9 DUP REMOVE L20 (0 DUPLICATES REMOVED)
L22           38 S L14 AND TYROSINE PHOSPHORYLATION
L23           14 DUP REMOVE L22 (24 DUPLICATES REMOVED)

=> s l11 and Flk-1
L24         1046 L11 AND FLK-1

=> s l24 and tyrosine
L25          394 L24 AND TYROSINE

=> s l25 and activation
L26          111 L25 AND ACTIVATION

=> s l26 and tyrosine phosphorylation
L27           35 L26 AND TYROSINE PHOSPHORYLATION

=> dup remove l27
PROCESSING COMPLETED FOR L27
L28           13 DUP REMOVE L27 (22 DUPLICATES REMOVED)

=> d l28 1-13 cbib abs
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L28 ANSWER 1 OF 13 MEDLINE on STN DUPLICATE 1
2005139563. PubMed ID: 15576436. Fluid shear stress induces differentiation of Flk-1-positive embryonic stem cells into vascular endothelial cells in vitro. Yamamoto Kimiko; Sokabe Takaaki; Watabe Tetsuro; Miyazono Kohei; Yamashita Jun K; Obi Syotaro; Ohura Norihiko; Matsushita Akiko; Kamiya Akira; Ando Joji. (Dept. of Biomedical Engineering, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan.) American journal of physiology. Heart and circulatory physiology, (2005 Apr) Vol. 288, No. 4, pp. H1915-24. Electronic Publication: 2004-12-02. Journal code: 100901228. ISSN: 0363-6135. Pub. country: United States. Language: English.

AB Pluripotent embryonic stem (ES) cells are capable of differentiating into all cell lineages, but the molecular mechanisms that regulate ES cell differentiation have not been sufficiently explored. In this study, we report that shear stress, a mechanical force generated by fluid flow, can induce ES cell differentiation. When Flk-1-positive (Flk-1(+)) mouse ES cells were subjected to shear stress, their cell density increased markedly, and a larger percentage of the cells were in the S and G(2)-M phases of the cell cycle than Flk -1(+) ES cells cultured under static conditions. Shear stress significantly increased the expression of the vascular endothelial cell-specific markers Flk-1, Flt-1, vascular endothelial cadherin, and PECAM-1 at both the protein level and the mRNA level, but it had no effect on expression of the mural cell marker smooth muscle alpha-actin, blood cell marker CD3, or the epithelial cell marker keratin. These findings indicate that shear stress selectively promotes the differentiation of Flk-1(+) ES cells into the endothelial cell lineage. The shear stressed Flk-1(+) ES cells formed tubelike structures in collagen gel and developed an extensive tubular network significantly faster than the static controls. Shear stress induced tyrosine phosphorylation of Flk-1 in Flk-1(+) ES cells that was blocked by a Flk-1 kinase inhibitor, SU1498, but not by a neutralizing antibody against VEGF. SU1498 also abolished the shear stress-induced proliferation and differentiation of Flk -1(+) ES cells, indicating that a ligand-independent activation of Flk-1 plays an important role in the shear stress-mediated proliferation and differentiation by Flk -1(+) ES cells.

L28 ANSWER 2 OF 13 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
2006:209847 Document No.: PREV200600211576. Vascular endothelial growth factor (VEGF) activates signal transducers and activators of transcription (STATs) proteins in human intestinal microvascular endothelial cells (HIMEC). Rafiee, Parvaneh; Theriot, Monica E.; Otterson, Mary F.; Binion, David G.. Gastroenterology, (APR 2005) Vol. 128, No. 4, Suppl. 2, pp. A516.
Meeting Info.: Annual Meeting of the American-Gastroenterological-Association/Digestive-Disease-Week. Chicago, IL, USA. May 14 -19, 2005. Amer Gastroenterol Assoc.
CODEN: GASTAB. ISSN: 0016-5085. Language: English.

AB INTRODUCTION: The angiogenic effect of VEGF is initiated by binding of the tyrosine kinase receptors, VEGFR1/Flt-1 and VEGFR2/Flk-1/KDR expressed on endothelial cells. Following receptor binding, VEGF activates various signaling cascades, including the mitogen activated protein kinase family (MAPKs) and PI3K/Akt, leading to cell cycle re-entry and proliferation of endothelial cells, including human gut specific microvascular endothetial cells (HIMEC). STAT proteins are important modulators of cell growth responses, and have recently been recognized to play a role in endothelial proliferation, but have not been characterized in human intestinal angiogenesis. We investigated the potential contribution of STATs signaling pathways activated by VEGF in HIMEC.METHODS: HIMEC monolayers were treated with VEGF, and nuclear translocation of STAT proteins was detected in nuclear protein extracts by an ELISA-based oligonucleotide binding assay containing an immobilized

STAT consensus binding site. By using antibodies against STAT1a, STAT3, STAT5A and STAT5B the STAT complex bound to oligonuleotide was detected. Addition of a secondary antibody conjugated to horseradish peroxidase resulted in a colorimetric readout that was quantified by spectrophotometer. The specific VEGFR2 blocking antibody was used to determine whether STATs activation were mediated through the VEGFR2/KDR receptor.RESULTS: VEGF induced tyrosine phosphorylation arid nuclear translocation of STAT1a, STAT3, STAT5A and SLAT 5B in HIMEC. Pre-treatment of HIMEC with VEGFR2 blocking antibody suppressed STATs phosphorylation and nuclear translocation. The p38 MAPK inhibitor SB203580 decreased STAT1a activation, whereas PD098059 (MEK/p44/42 MAPK inhibitor) suppressed both STAT1a and STAT3 in HIMEC. The tyorsine kinase inhibitor genistein blocked all STATs activation following VEGF stimulation of HIMEC.CONCLUSIONS: VEGF activates STATs pathways through VEGFR2/KDR receptor in HIMEC. The growth promoting activity of VEGF depends upon VEGFR2 activation in HIMEC. These findings suggest a role for the STATs in the regulation of gene expression associated with the angiogenic effects of VEGF in gut specific microvascular endothelial cells.

L28 ANSWER 3 OF 13 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

2005141462 EMBASE Fluid shear stress induces differentiation of Flk -1-positive embryonic stem cells into vascular endothelial cells in vitro. Yamamoto K.; Sokabe T.; Watabe T.; Miyazono K.; Yamashita J.K.; Obi S.; Ohura N.; Matsushita A.; Kamiya A.; Ando J.. J. Ando, Dept. of Biomedical Engineering, Graduate School of Medicine, Univ. of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan. joji@m.u-tokyo.ac.jp. American Journal of Physiology - Heart and Circulatory Physiology Vol. 288, No. 4 57-4, pp. H1915-H1924 2005.
Refs: 22.
ISSN: 0363-6135. CODEN: AJPPDI
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20050414. Last Updated on STN: 20050414

AB Pluripotent embryonic stem (ES) cells are capable of differentiating into all cell lineages, but the molecular mechanisms that regulate ES cell differentiation have not been sufficiently explored. In this study, we report that shear stress, a mechanical force generated by fluid flow, can induce ES cell differentiation. When Flk-1-positive (Flk-1(+)) mouse ES cells were subjected to shear stress, their cell density increased markedly, and a larger percentage of the cells were in the S and G(2)-M phases of the cell cycle than Flk -1(+) ES cells cultured under static conditions. Shear stress significantly increased the expression of the vascular endothelial cell-specific markers Flk-1, Flt-1, vascular endothelial cadherin, and PECAM-1 at both the protein level and the mRNA level, but it had no effect on expression of the mural cell marker smooth muscle α-actin, blood cell marker CD3, or the epithelial cell marker keratin. These findings indicate that shear stress selectively promotes the differentiation of Flk-1(+) ES cells into the endothelial cell lineage. The shear stressed Flk-1(+) ES cells formed tubelike structures in collagen gel and developed an extensive tubular network significantly faster than the static controls. Shear stress induced tyrosine phosphorylation of Flk-1 in Flk-1(+) ES cells that was blocked by a Flk-1 kinase inhibitor, SU1498, but not by a neutralizing antibody against VEGF. SU1498 also abolished the shear stress-induced proliferation and differentiation of Flk -1(+) ES cells, indicating that a ligand-independent activation of Flk-1 plays an important role in the shear stress-mediated proliferation and differentiation by Flk -1(+) ES cells.

L28 ANSWER 4 OF 13 MEDLINE on STN DUPLICATE 2
2003431778. PubMed ID: 12844492. Vascular endothelial growth factor regulates focal adhesion assembly in human brain microvascular endothelial cells through activation of the focal adhesion kinase and related adhesion focal tyrosine kinase. Avraham Hava Karsenty; Lee Tae-Hee; Koh Youngho; Kim Tae-Aug; Jiang Shuxian; Sussman Mark; Samarel Allen M; Avraham Shalom. (Division of Experimental Medicine and Hematology/Oncology, Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts 02115, USA.. savraham@bidmc.harvard.edu) . The Journal of biological chemistry, (2003 Sep 19) Vol. 278, No. 38, pp. 36661-8. Electronic Publication: 2003-07-03. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Vascular endothelial growth factor (VEGF) plays a significant role in blood-brain barrier breakdown and angiogenesis after brain injury. VEGF-induced endothelial cell migration is a key step in the angiogenic response and is mediated by an accelerated rate of focal adhesion complex assembly and disassembly. In this study, we identified the signaling mechanisms by which VEGF regulates human brain microvascular endothelial cell (HBMEC) integrity and assembly of focal adhesions, complexes comprised of scaffolding and signaling proteins organized by adhesion to the extracellular matrix. We found that VEGF treatment of HBMECs plated on laminin or fibronectin stimulated cytoskeletal organization and increased focal adhesion sites. Pretreating cells with VEGF antibodies or with the specific inhibitor SU-1498, which inhibits Flk-1/KDR receptor phosphorylation, blocked the ability of VEGF to stimulate focal adhesion assembly. VEGF induced the coupling of focal adhesion kinase (FAK) to integrin alphavbeta5 and tyrosine phosphorylation of the cytoskeletal components paxillin and p130cas. Additionally, FAK and related adhesion focal tyrosine kinase (RAFTK)/Pyk2 kinases were tyrosine -phosphorylated by VEGF and found to be important for focal adhesion sites. Overexpression of wild type RAFTK/Pyk2 increased cell spreading and the migration of HBMECs, whereas overexpression of catalytically inactive mutant RAFTK/Pyk2 markedly suppressed HBMEC spreading (approximately 70%), adhesion (approximately 82%), and migration (approximately 65%). Furthermore, blocking of FAK by the dominant-interfering mutant FRNK (FAK-related non-kinase) significantly inhibited HBMEC spreading and migration and also disrupted focal adhesions. Thus, these studies define a mechanism for the regulatory role of VEGF in focal adhesion complex assembly in HBMECs via activation of FAK and RAFTK/Pyk2.

L28 ANSWER 5 OF 13 MEDLINE on STN DUPLICATE 3
2003383885. PubMed ID: 12920240. Vascular endothelial growth factor expression, beta-catenin tyrosine phosphorylation, and endothelial proliferative behavior: a pathway for transformation?. Ilan Neta; Tucker Adeline; Madri Joseph A. (Department of Pathology, Yale University School of Medicine, New Haven, Connecticut 06520, USA.) Laboratory investigation; a journal of technical methods and pathology, (2003 Aug) Vol. 83, No. 8, pp. 1105-15. Journal code: 0376617. ISSN: 0023-6837. Pub. country: United States. Language: English.

AB The hypothesis that tumor growth is angiogenesis dependent has been documented by a considerable body of direct and indirect experimental data and has generated intense basic and pharmaceutical-related interest. In contrast, the study of endothelial cell tumors has been modest by comparison. Hemangioma is the most common tumor of any kind seen in infancy and also, perhaps, the least understood. We compared a mouse hemangioma-derived cell line (EOMA) and primary human endothelial cells (HUVEC) for their proliferative behavior and molecular alterations. EOMA cells intrinsically expressed vascular endothelial growth factor (VEGF), which acts in an autocrine manner, resulting in an increase in CD1 expression and cell proliferation, both of which were inhibited by anti-VEGF neutralizing antibodies. Such an autocrine loop is supported by constitutive VEGF receptor (Flk-1)

tyrosine phosphorylation, Flk-1 and
Flt-1 nuclear localization, and mitogen-activated protein kinase
activation. beta-catenin was also found to exhibit significant
nuclear localization and constitutively associate with Flk-
1 and Flt-1 in EOMA cells but much less so in HUVEC, and
immunoprecipitated Flk-1 was able to phosphorylate
purified beta-catenin in an immune complex kinase assay. EOMA cells were
also noted to express reduced levels of N-cadherin and gamma-catenin
compared with HUVEC. Interestingly, sequestration of endogenous VEGF in
EOMA cultures resulted in a dramatic decrease in nuclear beta-catenin and
a reduction in CD1 levels, whereas addition of exogenous VEGF elicited
increased nuclear beta-catenin localization and increased CD1 levels in
HUVEC. The possible contributions of VEGF signaling pathways, cell
junction component expression levels, and phosphorylation states to
endothelial cell transformation and proliferation are discussed.

L28 ANSWER 6 OF 13 MEDLINE on STN DUPLICATE 4
2002615068. PubMed ID: 12372815. Interplay between integrins and
FLK-1 in shear stress-induced signaling. Wang Yingxiao;
Miao Hui; Li Song; Chen Kuang-Den; Li Yi-Shuan; Yuan Suli; Shyy John Y-J;
Chien Shu. (Department of Bioengineering and Whitaker Institute of
Biomedical Engineering, University of California at San Diego, La Jolla,
California 92093, USA.) American journal of physiology. Cell physiology,
(2002 Nov) Vol. 283, No. 5, pp. C1540-7. Journal code: 100901225. ISSN:
0363-6143. Pub. country: United States. Language: English.
AB Blood flow can modulate vascular cell functions. We studied interactions
between integrins and Flk-1 in transducing the
mechanical shear stress due to flow. This application of a step shear
stress caused Flk-1. Casitas B-lineage lymphoma (Cbl)
activation (Flk-1. Cbl association,
tyrosine phosphorylation of the Cbl-bound Flk-
1, and tyrosine phosphorylation of Cbl) in
bovine aortic endothelial cells (BAECs). The activation of
integrins by plating BAECs on vitronectin or fibronectin also induced this
Flk-1. Cbl activation. The shear-induced
Flk-1. Cbl activation was blocked by
inhibitory antibodies for alphavbeta3- or beta1-integrin,
suggesting that it is mediated by integrins. Inhibition of Flk-
1 by SU1498 also abolished this shear-induced Flk-
1. Cbl activation. In contrast to the requirement of
integrins for Flk-1. Cbl activation, the
Flk-1 blocker SU1498 had no detectable effect on the
shear-induced integrin activation, suggesting that integrins and
Flk-1 play sequential roles in the signal transduction
hierarchy induced by shear stress. Integrins are essential for the
mechanical activation of Flk-1 by shear
stress but not for the chemical activation of Flk-
1 by VEGF.

L28 ANSWER 7 OF 13 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights
reserved on STN
2002371129 EMBASE Interplay between integrins and FLK-1
in shear stress-induced signaling. Wang Y.; Miao H.; Li S.; Chen K.-D.; Li
Y.-S.; Yuan S.; Shyy J.Y.-J.; Chien S.. S. Chien, Dept. of Bioengineering,
Univ. of California, San Diego, San Diego, CA 92093-0427, United States.
shuchien@ucsd.edu. American Journal of Physiology - Cell Physiology Vol.
283, No. 5 52-5, pp. C1540-C1547 2002.
Refs: 43.
ISSN: 0363-6143. CODEN: AJPCDD
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20021107. Last Updated on STN: 20021107
AB Blood flow can modulate vascular cell functions. We studied interactions
between integrins and Flk-1 in transducing the
mechanical shear stress due to flow. This application of a step shear
stress caused Flk-1.ovrhdot.Casitas B-lineage lymphoma

(Cbl) activation (Flk-1.ovrhdot.Cbl association, tyrosine phosphorylation of the Cbl-bound Flk-1, and tyrosine phosphorylation of Cbl) in bovine aortic endothelial cells (BAECs). The activation of integrins by plating BAECs on vitronectin or fibronectin also induced this Flk-1.ovrhdot.Cbl activation. The shear-induced Flk-1 .ovrhdot.Cbl activation was blocked by inhibitory antibodies for α(v)β(3)- or β(1)-integrin, suggesting that it is mediated by integrins. Inhibition of Flk-1 by SU1498 also abolished this shear-induced Flk-1.ovrhdot.Cbl activation. In contrast to the requirement of integrins for Flk-1.ovrhdot.Cbl activation, the Flk-1 blocker SU1498 had no detectable effect on the shear-induced integrin activation, suggesting that integrins and Flk-1 play sequential roles in the signal transduction hierarchy induced by shear stress. Integrins are essential for the mechanical activation of Flk-1 by shear stress but not for the chemical activation of Flk-1 by VEGF.

L28 ANSWER 8 OF 13 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

2000:537281 The Genuine Article (R) Number: 332QG. Vascular endothelial growth factor up-regulates ICAM-1 expression via the phosphatidylinositol 3 OH-kinase/AKT/nitric oxide pathway and modulates migration of brain microvascular endothelial cells. Radisavljevic Z; Avraham H; Avraham S (Reprint). Harvard Univ, Sch Med, Inst Med, Beth Israel Deaconess Med Ctr, Dept Med, Div Expt Med, 4 Blackfan Circle, Boston, MA 02115 USA (Reprint); Harvard Univ, Sch Med, Inst Med, Beth Israel Deaconess Med Ctr, Dept Med, Div Expt Med, Boston, MA 02115 USA. JOURNAL OF BIOLOGICAL CHEMISTRY (7 JUL 2000) Vol. 275, No. 27, pp. 20770-20774. ISSN: 0021-9258. Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Endothelium of the cerebral blood microvessels, which constitutes the major component of the blood-brain barrier, controls leukocyte and metastatic cancer cell adhesion and trafficking into the brain parenchyma. In this study, using rat primary brain microvascular endothelial cells (BMEC), we demonstrate that the vascular endothelial growth factor (VEGF), a potent promoter of angiogenesis, up-regulates the expression of the intracellular adhesion molecule-1 (ICAM-1) through a novel pathway that includes phosphatidylinositol 3 OH-kinase (PI3K), AKT, and nitric oxide (NO), resulting in the migration of BMEC. Upon VEGF treatment, AKT is phosphorylated in a PI3K-dependent manner. AKT activation leads to NO production and release and activation-deficient AKT attenuates NO production stimulated by VEGF. Transfection of the constitutive myr-AKT construct significantly increased basal NO release in BMEC. In these cells, VEGF and the endothelium-derived NO synergistically up-regulated the expression of ICAM-1, which was mediated by the PI3K pathway. This activity was blocked by the PI3K-specific inhibitor, wortmannin, Furthermore, VEGF and NO significantly increased BmEC migration, which was mediated by the up-regulation of ICAM-1 expression and was dependent on the integrity of the PI3K/AKT/NO pathway. This effect was abolished by wortmannin, by the specific ICAM-1 antibody, by the specific inhibitor of NO synthase, N-G-L-monomethyl-arginine (L-NMMA) or by a combination of wortmannin, ICAM-1 antibody, and L-NMMA. These findings demonstrate that the angiogenic factor VEGF up-regulates ICAM-1 expression and signals to ICAM-1 as an effector molecule through the PI3K/AKT/NO pathway, which leads to brain microvessel endothelial cell, migration. These observations may contribute to a better understanding of BMEC angiogenesis and the physiological as well as pathophysiological function of the blood-brain barrier, whose integrity is crucial for normal brain function.

L28 ANSWER 9 OF 13 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

2000:786248 The Genuine Article (R) Number: 361VJ. Design of GFB-111, a platelet-derived growth factor binding molecule with antiangiogenic and anticancer activity against human tumors in mice. Blaskovich M A; Lin Q; Delarue F L; Sun J; Park H S; Coppola D; Hamilton A D; Sebti S M (Reprint) . Univ S Florida, H Lee Moffit Canc Ctr & Res Inst, Dept Biochem & Mol Biol, Drug Discovery Program, Tampa, FL 33612 USA (Reprint); Univ S Florida, Dept Pathol, Tampa, FL 33612 USA; Yale Univ, Dept Chem, New Haven, CT 06511 USA. NATURE BIOTECHNOLOGY (OCT 2000) Vol. 18, No. 10, pp. 1065-1070. ISSN: 1087-0156. Publisher: NATURE AMERICA INC, 345 PARK AVE SOUTH, NEW YORK, NY 10010-1707 USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We have designed a molecule, GFB-111, that binds to platelet-derived growth factor (PDGF), prevents it from binding to its receptor tyrosine kinase, and blocks PDGF-induced receptor autophosphorylation, activation of Erk1 and Erk2 kinases, and DNA synthesis. GFB-111 is highly potent (IC50 = 250 nM) and selective for PDGF over EGF, IGF-1, aFGF, bFGF, and HRG beta (IC50 values > 100 mu M), but inhibits VEGF-induced Flk-1 tyrosine phosphorylation and Erk1/Erk2 activation with an IC50 of 10 mu M. GFB-111 treatment of nude mice bearing human tumors resulted in significant inhibition of tumor growth and angiogenesis. The results demonstrate the feasibility of designing novel growth factor-binding molecules with potent anticancer and antiangiogenic activity.

L28 ANSWER 10 OF 13 MEDLINE on STN DUPLICATE 5

1999443794. PubMed ID: 10512875. A role for cadherin-5 in regulation of vascular endothelial growth factor receptor 2 activity in endothelial cells. Rahimi N; Kazlauskas A. (Boston University, School of Medicine, Boston, Massachusetts 02028, USA.) Molecular biology of the cell, (1999 Oct) Vol. 10, No. 10, pp. 3401-7. Journal code: 9201390. ISSN: 1059-1524. Pub. country: United States. Language: English.

AB FLK-1/vascular endothelial growth factor receptor 2 (VEGFR-2) is one of the receptors for VEGF. In this study we examined the effect of cell density on activation of VEGFR-2. VEGF induces only very slight tyrosine phosphorylation of VEGFR-2 in confluent (95-100% confluent) pig aortic endothelial (PAE) cells. In contrast, robust VEGF-dependent tyrosine phosphorylation of VEGFR-2 was observed in cells plated in sparse culture conditions (60-65% confluent). A similar cell density-dependent phenomenon was observed in different endothelial cells but not in NIH-3T3 fibroblast cells expressing VEGFR-2. Stimulating cells with high concentrations of VEGF or replacing the extracellular domain of VEGFR-2 with that of the colony-stimulating factor 1 receptor did not alleviate the sensitivity of VEGFR-2 to cell density, indicating that the confluent cells were probably not secreting an antagonist to VEGF. Furthermore, in PAE cells, ectopically introduced platelet-derived growth factor alpha receptor could be activated at both high and low cell density conditions, indicating that the density effect was not universal for all receptor tyrosine kinases expressed in endothelial cells. In addition to lowering the density of cells, removing divalent cations from the medium of confluent cells potentiated VEGFR-2 phosphorylation in response to VEGF. These findings suggested that cell-cell contact may be playing a role in regulating the activation of VEGFR-2. To this end, pretreatment of confluent PAE cells with a neutralizing anti-cadherin-5 antibody potentiated the response of VEGFR-2 to VEGF. Our data demonstrate that endothelial cell density plays a critical role in regulating VEGFR-2 activity, and that the underlying mechanism appears to involve cadherin-5.

L28 ANSWER 11 OF 13 MEDLINE on STN DUPLICATE 6

1999137695. PubMed ID: 9950855. Role of phospholipase C, protein kinase C, and calcium in VEGF-induced venular hyperpermeability. Wu H M; Yuan Y; Zawieja D C; Tinsley J; Granger H J. (Departments of Medical Physiology

and Surgery, Texas A & M University System Health Science Center, Temple, Texas 76504, USA.) The American journal of physiology, (1999 Feb) Vol. 276, No. 2 Pt 2, pp. H535-42. Journal code: 0370511. ISSN: 0002-9513. Pub. country: United States. Language: English.

AB We previously demonstrated that vascular endothelial growth factor (VEGF)-elicited increase in the permeability of coronary venules was blocked by the nitric oxide (NO) synthase inhibitor NG-monomethyl-L-arginine (L-NMMA). The aim of this study was to delineate in more detail the signaling pathways upstream from NO production in VEGF-induced venular hyperpermeability. The apparent permeability coefficient of albumin (Pa) and endothelial cytosolic Ca2+ concentration ([Ca2+]i) were measured in intact perfused porcine coronary venules using fluorescence microscopy. VEGF (10(-10) M) induced a two- to threefold increase in Pa, which was blocked by a monoclonal antibody directed against the VEGF receptor Flk-1/KDR, the phospholipase C (PLC) antagonist U-73122, or the protein kinase C (PKC) antagonist bisindolylmaleimide (BIM). In 12 venules that displayed the [Ca2+]i response to bradykinin (10(-6) M) and ionomycin (10(-6) M), only 4 vessels responded to VEGF with a transient increase in [Ca2+]i. Furthermore, Western blot analysis of cultured human umbilical vein endothelial cells showed that VEGF increased tyrosine phosphorylation of PLC-gamma and serine phosphorylation of endothelial constitutive NO synthase (ecNOS). The hyperphosphorylation of PLC-gamma was greatly attenuated by the KDR receptor antibody and U-73122, but not by BIM or L-NMMA. In contrast, U-73122 and BIM were able to inhibit VEGF-elicited serine phosphorylation of ecNOS. The results suggest that VEGF induces venular hyperpermeability through a KDR receptor-mediated activation of PLC. In turn, ecNOS is activated by PLC-mediated PKC and/or cytosolic Ca2+ elevation stimulation.

L28 ANSWER 12 OF 13 EMBASE

1999078512 EMBASE Role of phospholipase C, protein kinase C, and calcium in VEGF-induced venular hyperpermeability. Wu H.M.; Yuan Y.; Zawieja D.C.; Tinsley J.; Granger H.J.. H.M. Wu, Dept. of Medical Physiology, Texas A and M Univ. Hlth. Sci. Ctr., Bldg. 4, 1901 South First St., Temple, TX 76504, United States. American Journal of Physiology - Heart and Circulatory Physiology Vol. 276, No. 2 45-2, pp. H535-H542 1999. Refs: 34.
ISSN: 0363-6135. CODEN: AJPPDI
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 19990326. Last Updated on STN: 19990326

AB We previously demonstrated that vascular endothelial growth factor (VEGF)-elicited increase in the permeability of coronary venules was blocked by the nitric oxide (NO) synthase inhibitor N(G)-monomethyl-L-arginine (L- NMMA). The aim of this study was to delineate in more detail the signaling pathways upstream from NO production in VEGF-induced venular hyperpermeability. The apparent permeability coefficient of albumin (P(a)) and endothelial cytosolic Ca2+ concentration ([Ca2+](i)) were measured in intact perfused porcine coronary venules using fluorescence microscopy. VEGF (10-10 M) induced a two- to threefold increase in P(a), which was blocked by a monoclonal antibody directed against the VEGF receptor Flk-1/KDR, the phospholipase C (PLC) antagonist U-73122, or the protein kinase C (PKC) antagonist bisindolylmaleimide (BIM). In 12 venules that displayed the [Ca2+](i) response to bradykinin (10-6 M) and ionomycin (10-6 M), only 4 vessels responded to VEGF with a transient increase in [Ca2+](i). Furthermore, Western blot analysis of cultured human umbilical vein endothelial cells showed that VEGF increased tyrosine phosphorylation of PLC- γ and serine phosphorylation of endothelial constitutive NO synthase (ecNOS). The hyperphosphorylation of PLC-γ was greatly attenuated by the KDR receptor antibody and U-73122, but not by BIM or L-NMMA. In contrast, U- 73122 and BIM were able to inhibit VEGF-elicited serine phosphorylation of ecNOS. The results suggest that VEGF induces venular hyperpermeability through a KDR receptor-mediated

activation of PLC. In turn, ecNOS is activated by PLC-mediated PKC and/or cytosolic Ca2+ elevation stimulation.

L28 ANSWER 13 OF 13 MEDLINE on STN DUPLICATE 7
97409624. PubMed ID: 9263985. Receptor protein tyrosine kinases in perinatal developing rat kidney. Kee N; McTavish A J; Papillon J; Cybulsky A V. (Department of Medicine, Royal Victoria Hospital, Montreal, Quebec, Canada.) Kidney international, (1997 Aug) Vol. 52, No. 2, pp. 309-17. Journal code: 0323470. ISSN: 0085-2538. Pub. country: United States. Language: English.

AB We have identified receptor protein tyrosine kinases (PTKs) that are expressed and/or activated during kidney development. mRNA from fetal rat kidneys in late gestation (embryonic day 21), was used to prepare a cDNA template for polymerase chain reaction amplification with primers based on conserved regions of PTKs, and products were subcloned and sequenced. Among 346 clones, we identified epidermal growth factor receptor (EGF-R), Tie-2, platelet-derived growth factor receptor (PDGF-R)-alpha, PDGF-R beta, Flk-1, Flt-4, fibroblast growth factor receptor (FGF-R)-1, FGF-R3, FGF-R4, Met, and RYK/Nbtk-1. PTK expression was studied by immunoprecipitation and immunoblotting of kidney membrane proteins with specific antibodies. EGF-R, PDGF-R alpha, FGF-R1, FGF-R3, Met, and in some cases Tie-2 protein expression was greater in fetal kidneys, as compared with kidneys from 12-week-old adult rats (controls). Flk-1, PDGF-R beta, and FGF-R4 proteins were expressed comparably, however, Flt-4 was not detected. As a reflection of receptor PTK activity, we assessed endogenous tyrosine phosphorylation, and in vitro autophosphorylation. EGF-R and PDGF-R alpha displayed activity in fetal, but not adult kidneys. FGF-R3 and Flk-1 were active in some fetal kidneys, and the other PTKs were not active. Thus, in late gestational rat kidney, there are distinct patterns of receptor PTK expression and activity. EGF-R, PDGF-R alpha, FGF-R3 and Flk-1 are among the PTKs that are activated, and they may mediate perinatal development of renal epithelial, interstitial, or vascular structures.

=> s l11 and anti-phosphorylated tyrosine
L29 11 L11 AND ANTI-PHOSPHORYLATED TYROSINE

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PROCESSING COMPLETED FOR L29
L30 8 DUP REMOVE L29 (3 DUPLICATES REMOVED)

=> d l30 1-8 cbib abs

L30 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN
2006:498791 Document No. 145:332262 Study on interaction between apoptosis-inducing factor and non-receptor tyrosine kinase c-Abl. Wang, Chang-zheng; Chen, Dong-li; Cao, Cheng; Ma, Qing-jun (Institute of Biotechnology, Academy of Military Medical Sciences, Beijing, 100850, Peop. Rep. China). Shengwu Jishu Tongxun, 17(2), 152-154 (Chinese) 2006. CODEN: SJTHB6. ISSN: 1009-0002. Publisher: Shengwu Jishu Tongxun Bianjibu.

AB This paper investigated the interaction between apoptosis-inducing factor (AIF) and non-receptor tyrosine kinase c-Abl. The protein interaction was demonstrated by immuno-copptn., and protein phosphorylation was analyzed with anti-phosphorylated tyrosine antibody. Protein expression levels were investigated with green fluorescent protein plasmid transfection. The results showed that AIF and c-Abl could form complex, and c-Abl could phosphorylate AIF and increase its expression level.

L30 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN
2005:235433 Document No. 142:294302 Method for detecting phosphorylated

protein. Nakanishi, Hisao (Sumitomo Bakelite Co., Ltd., Japan). Jpn. Kokai Tokkyo Koho JP 2005069788 A2 20050317, 5 pp. (Japanese). CODEN: JKXXAF. APPLICATION: JP 2003-298048 20030822.

AB A method is provided for safely and rapidly detecting a phosphorylated substance to be trapped with high sensitivity and high efficiency. The method comprises immobilizing on a baseplate surface a trapping substance capable of trapping a biomol., specifically trapping the biomol. to be trapped (e.g., protein, peptide) by the interaction with the trapping substance, and determining the presence or absence of phosphorylation with the trapped biomol. Preferably, the trapping substance contains either one of protein, peptide, or nucleic acid while the protein as a trapping substance is an antibody to a phosphorylated protein (e.g., anti-phosphorylated serine antibody, anti-phosphorylated threonine antibody, or anti-phosphorylated tyrosine antibody).

L30 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN

2005:120071 Document No. 142:193898 Phosphorylated protein purification device/method using antibody. Shimaoka, Hideyuki (Sumitomo Bakelite Co., Ltd., Japan). Jpn. Kokai Tokkyo Koho JP 2005035891 A2 20050210, 8 pp. (Japanese). CODEN: JKXXAF. APPLICATION: JP 2003-196898 20030715.

AB A protein purification device is provided, with which only phosphorylated proteins are specifically purified and recovered from a sample solution such as a cell homogenate containing various kinds of proteins by a convenient method. The device possesses a structure for allowing a sample solution such as a cell homogenate containing various kinds of proteins to flow in a flow path created in the device, and the flow path is equipped in its part or entirety with a trapping part for specifically trapping phosphorylated proteins only. Preferably, the trapping part possesses an anti-phosphorylated serine antibody, an anti-phosphorylated threonine antibody and an anti-phosphorylated tyrosine antibody immobilized on it.

L30 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN

2004:965379 Document No. 141:406043 Method for identifying Bcl2L12 polypeptide activators and inhibitors in relation to cancer treatment. Stegh, Alex; Kim, Hyunggee; Depinho, Ronald A.; Chin, Lynda (Dana-Farber Cancer Institute, Inc., USA). PCT Int. Appl. WO 2004096991 A2 20041111, 80 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US12591 20040423. PRIORITY: US 2003-465573P 20030425.

AB The invention provides methods and materials related to Bc12L12 polypeptides and the biol. activities of Bc12L12 polypeptides. For example, the invention provides methods and materials related to identifying activators and inhibitors of Bc12L12 polypeptide activities such as the ability to block apoptosis and promote cell growth and transformation. The invention also provides methods and materials for treating mammals having cancer.

L30 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN

2004:1103663 Document No. 142:389706 Interaction between non-receptor tyrosine kinase c-Abl and Siva-1 in cell apoptosis. Li, Ping; Li, Chufang; Liu, Xuan; Jin, Yanwen; Huang, Wei; Yi, Yanping; Ma, Qingjun; Kufe, Donald W.; Cao, Cheng (Beijing Institute of Biotechnology, Beijing, 100850, Peop. Rep. China). Junshi Yixue Kexueyuan Yuankan, 27(4), 251-254 (Chinese) 2003. CODEN: JYKYEL. ISSN: 1000-5501. Publisher: Junshi Yixue Kexueyuan Yuankan Bianjibu.

AB The interaction between non-receptor tyrosine kinase c-Abl and apoptosis inducing protein Siva-1 was studied. Interaction was demonstrated by immunopptn., in vivo tyrosine phosphorylation was analyzed by immuno-blotting with anti- phosphorylated tyrosine antibody, in vitro phosphorylation was analyzed by in vitro kinase assay and apoptosis was evaluated by the percentage of sub G1 cells by FACScan. Interaction of c-Abl with Siva-1 was demonstrated by immuno-copptn. and direct binding anal. C-Abl bound to Siva-1 by its SH3 domain. Siva-1 could be phosphorylated by c-Abl in vitro or in vivo. Siva-1 cannot induce apoptosis in c-Abl(K-R) dominant neg. cell line. Phosphorylation of Siva-1 by c-Abl plays an important role in Siva-1 induced apoptosis.

L30 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN
1999:289332 Document No. 131:72555 Induced phosphorylation and activation of JAK-3 in CTCL cells by interleukin-7. Dong, Ziming; Yang, Hongyan; Zhang, Yiguo; Zhao, Mingyao; Zheng, Zhimin; Berger, Carole; Wang, Nianci (Department of Pathophysiology, Henan Medical University, Zhengzhou, 450052, Peop. Rep. China). Henan Yike Daxue Xuebao, 34(1), 14-18 (Chinese) 1999. CODEN: HEYDE2. ISSN: 1000-1069. Publisher: Henan Yike Daxue Xuebao Bianjibu.

AB To study induced phosphorylation and activation of JAK-3 in cutaneous T-cell lymphoma (CTCL) by interleukin-7 (IL-7). IL-7 stimulates proliferation of several benign and malignant lymphocyte populations including tumor cells from patients with CTCL. The Janus family of kinases (JAKs) has been shown to be involved in the signal transduction of a number of cytokine receptors. A novel JAK family member JAK-3, which is expressed in natural killer (NK) and activated T cells, is coupled functionally and phys. with the interleukin-2 (IL-2) receptor (IL-2R) in those cells. Cells isolated from peripheral blood of CTCL patients were treated with IL-7 in vitro for 1, 5, 10, 15 and 20 min, resp. Immunopptg. the lysates was performed with anti-JAK-3 and anti-p59fyn antibodies and Western blotting with anti-phosphorylated tyrosine and anti-JAK-3 antibodies. IL-7 induced tyrosine phosphorylation of JAK-3 in CTCL cells. Anti-p59fyn antibody co-immunopptd. with JAK-3. But it was not found that IL-12 could induce phosphorylation of JAK-3. These results suggest that IL-7 may play a role in pathophysiol. of CTCL, and indicate that the IL-7 receptor (IL-7R) mediates the activation of the tyrosine phosphorylation signal transduction pathway.

L30 ANSWER 7 OF 8 MEDLINE on STN DUPLICATE 1
1998221560. PubMed ID: 9560789. Growth inhibitory effect of bovine lactoferrin to Toxoplasma gondii tachyzoites in murine macrophages: tyrosine phosphorylation in murine macrophages induced by bovine lactoferrin. Tanaka T; Omata Y; Isamida T; Saito A; Shimazaki K; Yamauchi K; Suzuki N. (Department of Veterinary Physiology, Obihiro University of Agriculture and Veterinary Medicine, Japan.) The Journal of veterinary medical science / the Japanese Society of Veterinary Science, (1998 Mar) Vol. 60, No. 3, pp. 369-71. Journal code: 9105360. ISSN: 0916-7250. Pub. country: Japan. Language: English.

AB Previous studies have shown that lactoferrin induces growth inhibitory effects in mouse macrophages against intracellular Toxoplasma gondii, and these effects were not mediated by the oxygen-dependent and inorganic nitrogen-dependent pathway. To clarify the mechanism of anti-Toxoplasma gondii activity induced by lactoferrin, we examined whether lactoferrin promoted the phosphorylation of tyrosine residues in macrophage proteins. In immunoblotting assays using anti-[phosphorylated tyrosine] monoclonal antibody, phosphorylation of tyrosine residues was detected in protein(s) of approximately 30 kDa in macrophages incubated with lactoferrin. Inhibition of the lactoferrin-induced tyrosine-phosphorylation by genistein led to loss of the lactoferrin-induced growth inhibitory effect against the parasites. These findings suggest that lactoferrin induces tyrosine-phosphorylation in macrophages, and the tyrosine-phosphorylation seems to be associated

with the induction of the growth inhibitory activity exerted against intracellular Toxoplasma gondii.

L30 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN
1994:652666 Document No. 121:252666 Diagnosis of Ph1 positive acute lymphoblastic leukemia using anti-phosphorylated tyrosine antibody. Sugita, Kanji; Nakazawa, Shinpei (Yamanashi Med. Coll., Yamanashi, 409-38, Japan). Igaku no Ayumi, 170(11), 966-8 (Japanese) 1994. CODEN: IGAYAY. ISSN: 0039-2359.
AB A review, with 2 refs., on the different diagnosis of masked Ph1-acute lymphoblastic leukemia (ALL) in pediatric common ALL based on elevated phosphorylation of tyrosine residues due to formation of KCL-ALL fused protein. The method picks up masked Ph1-ALL to the treated intensively from standard risk ALL group.

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L32 5 L31 AND ANTIBOD?

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L33 5 L32 AND KDR

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'REOMVE' IS NOT VALID. VALID FILE NAMES ARE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS'
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The file names of duplicates that can be kept are listed above.
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L34 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2006 ACS on STN
2003:757736 Document No. 139:240839 The use of an epitope of vascular endothelial growth factor receptor KDR/Flk-1 for the screening of KDR/Flk-1-modulating drugs. Cartlidge, Sue Ann (Astrazeneca AB, Swed.; Astrazeneca Uk Limited). PCT Int. Appl. WO 2003078465 A1 20030925, 26 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-GB991 20030311. PRIORITY: GB 2002-6072 20020315.
AB The present invention relates to the use of the epitope which comprises the tyrosine at position 1214 in the amino acid sequence of the vascular endothelial growth factor receptor, KDR/Flk-1, as a marker in the measurement of a change in the activation state of the KDR /Flk-1 receptor and to probes, such as antibodies, which recognize said epitope. The invention also relates to the use of KDR/Flk-1 epitope Y1214 as a marker in the detection of and/or measurement of the level of the KDR/Flk-1 receptor and to assays which utilize the use of the Y1214 epitope and to compds. derived from said assays.

L34 ANSWER 2 OF 2 MEDLINE on STN DUPLICATE 1
2003352024. PubMed ID: 12823710. The angiogenic receptor KDR is widely distributed in human tissues and tumours and relocates intracellularly on phosphorylation. An immunohistochemical study. Stewart M; Turley H; Cook N; Pezzella F; Pillai G; Ogilvie D; Cartlidge S ; Paterson D; Copley C; Kendrew J; Barnes C; Harris A L; Gatter K C. (Cancer Research UK Tumour Pathology Group, Nuffield Department of Clinical Laboratory Sciences, University of Oxford, John Radcliffe Hospital, Oxford, OX3 9DU, UK.) Histopathology, (2003 Jul) Vol. 43, No. 1, pp. 33-9. Journal code: 7704136. ISSN: 0309-0167. Pub. country: England: United Kingdom. Language: English.

AB AIMS: Angiogenesis is an important factor in tumour growth and metastasis. Vascular endothelial growth factor receptor 2 (VEGFR-2) or KDR plays a crucial role in angiogenesis. The aim of this study was to raise and characterize antibodies against phosphorylated KDR which could be used for studies on human tissues to assess KDR activation and novel inhibitors of KDR activation in clinical trials. METHODS AND RESULTS: Three monoclonal antibodies and one rabbit polyclonal antiserum were produced. The specificity of the antibodies was confirmed by ELISA. One of the mouse antibodies and the rabbit polyclonal antiserum reacted with a 200-kDa band on a Western blot of human umbilical vein endothelial cell (HUVEC) lysates, the molecular weight of KDR. Immunohistochemical staining showed that phosphorylated KDR is present in a wide variety of normal tissues including liver, colon and placenta, and is not restricted to endothelium. It was also present in a number of human tumours including breast carcinomas, colonic carcinomas and non-Hodgkin's lymphomas. The pattern of staining was membranous, cytoplasmic and nuclear. CONCLUSIONS: This study has shown that phosphorylated KDR is present in a wide variety of tumour and tissue types and is not confined to endothelium.

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L35 5 L31 AND KDR

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=> d l36 1-2 cbib abs

L36 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2006 ACS on STN
2003:757736 Document No. 139:240839 The use of an epitope of vascular endothelial growth factor receptor KDR/Flk-1 for the screening of KDR/Flk-1-modulating drugs. Cartlidge, Sue Ann (Astrazeneca AB, Swed.; Astrazeneca Uk Limited). PCT Int. Appl. WO 2003078465 A1 20030925, 26 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-GB991 20030311. PRIORITY: GB 2002-6072 20020315.

AB The present invention relates to the use of the epitope which comprises the tyrosine at position 1214 in the amino acid sequence of the vascular endothelial growth factor receptor, KDR/Flk-1, as a marker in the measurement of a change in the activation state of the KDR /Flk-1 receptor and to probes, such as antibodies, which recognize said epitope. The invention also relates to the use of KDR/Flk-1 epitope Y1214 as a marker in the detection of and/or measurement of the level of the KDR/Flk-1 receptor and to assays which utilize the use of the Y1214 epitope and to compds. derived from said assays.

L36 ANSWER 2 OF 2 MEDLINE on STN DUPLICATE 1
2003352024. PubMed ID: 12823710. The angiogenic receptor KDR is widely distributed in human tissues and tumours and relocates intracellularly on phosphorylation. An immunohistochemical study. Stewart M; Turley H; Cook N; Pezzella F; Pillai G; Ogilvie D; Cartlidge S ; Paterson D; Copley C; Kendrew J; Barnes C; Harris A L; Gatter K C. (Cancer Research UK Tumour Pathology Group, Nuffield Department of Clinical Laboratory Sciences, University of Oxford, John Radcliffe Hospital, Oxford, OX3 9DU, UK.) Histopathology, (2003 Jul) Vol. 43, No. 1, pp. 33-9. Journal code: 7704136. ISSN: 0309-0167. Pub. country: England: United Kingdom. Language: English.

AB AIMS: Angiogenesis is an important factor in tumour growth and metastasis. Vascular endothelial growth factor receptor 2 (VEGFR-2) or KDR plays a crucial role in angiogenesis. The aim of this study was to raise and characterize antibodies against phosphorylated KDR which could be used for studies on human tissues to assess KDR activation and novel inhibitors of KDR activation in clinical trials. METHODS AND RESULTS: Three monoclonal antibodies and one rabbit polyclonal antiserum were produced. The specificity of the antibodies was confirmed by ELISA. One of the mouse antibodies and the rabbit polyclonal antiserum reacted with a 200-kDa band on a Western blot of human umbilical vein endothelial cell (HUVEC) lysates, the molecular weight of KDR . Immunohistochemical staining showed that phosphorylated KDR is present in a wide variety of normal tissues including liver, colon and placenta, and is not restricted to endothelium. It was also present in a number of human tumours including breast carcinomas, colonic carcinomas and non-Hodgkin's lymphomas. The pattern of staining was membranous, cytoplasmic and nuclear. CONCLUSIONS: This study has shown that phosphorylated KDR is present in a wide variety of tumour and tissue types and is not confined to endothelium.

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	234.59	234.80

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-18.00	-18.00

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 03/00991

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K14/71 A61K39/00 G01N33/53 C07K16/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K A61K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
MEDLINE, BIOSIS, EPO-Internal, EMBASE, CHEM ABS Data, LIFESCIENCES, CANCERLIT, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WOOD J M ET AL: "PTK787/ZK 222584, a novel and potent inhibitor of vascular endothelial growth factor receptor tyrosine kinases, impairs vascular endothelial growth factor-induced responses and tumor growth after oral administration." CANCER RESEARCH. UNITED STATES 15 APR 2000, vol. 60, no. 8, 15 April 2000 (2000-04-15), pages 2178-2189, XP000971163 ISSN: 0008-5472 abstract --- -/--	11

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 August 2003	01/09/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Renggli-Zulliger, N

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 03/00991

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	IGARASHI KATSUHIDE ET AL: "Tyrosine 1213 of Flt-1 is a major binding site of Nck and SHP-2." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 246, no. 1, 8 May 1998 (1998-05-08), pages 95-99, XP002251094 ISSN: 0006-291X page 98, right-hand column, last paragraph -page 99; figures 2-4 ---	1-14
Y	CARROLL RONA S ET AL: "KDR activation in astrocytic neoplasms." CANCER, vol. 86, no. 7, 1 October 1999 (1999-10-01), pages 1335-1341, XP002251095 ISSN: 0008-543X abstract ---	1-14
Y	TAKAHASHI T ET AL: "A single autophosphorylation site on KDR/Flk-1 is essential for VEGF-A-dependent activation of PLC-gamma and DNA synthesis in vascular endothelial cells." THE EMBO JOURNAL. ENGLAND 1 JUN 2001, vol. 20, no. 11, 1 June 2001 (2001-06-01), pages 2768-2778, XP002251096 ISSN: 0261-4189 cited in the application abstract; figure 1 page 2769, left-hand column, paragraph 1 ---	1-14
A	MENRAD A ET AL: "NOVEL ANTIBODIES DIRECTED AGAINST THE EXTRACELLULAR DOMAIN OF THE HUMAN VEGF-RECEPTOR TYPE II" HYBRIDOMA, LIEBERT, NEW YORK, NY, US, vol. 16, no. 5, 1 October 1997 (1997-10-01), pages 465-471, XP002052460 ISSN: 0272-457X abstract page 469 --- -/--	1-14

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 03/00991

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ZHU Z ET AL: "Inhibition of vascular endothelial growth factor induced mitogenesis of human endothelial cells by a chimeric anti-kinase insert domain-containing receptor antibody." CANCER LETTERS. IRELAND 1 MAR 1999, vol. 136, no. 2, 1 March 1999 (1999-03-01), pages 203-213, XP002251097 ISSN: 0304-3835 abstract page 210, left-hand column, last paragraph -right-hand column ---	1-14
A	ROCKWELL P ET AL: "IN VITRO NEUTRALIZATION OF VASCULAR ENDOTHELIAL GROWTH FACTOR ACTIVATION OF FLK-1 BY A MONOCLONAL ANTIBODY" MOLECULAR AND CELLULAR DIFFERENTIATION, CRC PRESS, BOCA RATON, US, vol. 3, no. 1, 1995, pages 91-109, XP002052455 ISSN: 1065-3074 page 102, paragraphs 2,3 abstract ---	1-14
P,X	MEYER ROSANA D ET AL: "The presence of a single tyrosine residue at the carboxyl domain of vascular endothelial growth factor receptor-2/FLK-1 regulates its autophosphorylation and activation of signaling molecules." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 277, no. 30, 22 May 2002 (2002-05-22), pages 27081-27087, XP002251098 July 28, 2002 ISSN: 0021-9258 abstract; figures 1,4-6 -----	1-14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 03/00991

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 9-11(partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II *Observations where unity of invention is lacking (Continuation of item 2 of first sheet)*

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 9-11(partially)

Present claims 9-11 relate to a product defined by reference to a desirable characteristic or property, namely comprising an inhibitor.

The claim covers all products having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products. In the present case, the claim so lacks support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search could not be carried out for the inhibitors disclosed in the present application since not a single example of such a substance is disclosed not even in example 2 where only inhibitors as a generic term are mentioned. The search has been restricted to antibodies and some chemical compounds (incomplete) that are inhibitors of the KDR/Flk-1 receptor.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

WEST Search History

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DATE: Wednesday, November 15, 2006

Hide?	Set Name	Query	Hit Count
		DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR	
☐	L37	L35 and 1214	2
☐	L36	L35 and Y1214	0
☐	L35	L34 and (KDR)same(Flk-1)	122
☐	L34	L30 nnd (phosphorylated)adj(tyrosine)adj(residue)	36932
☐	L33	L31 and Flk-1	3
☐	L32	L31 and KDR	3
☐	L31	L30 and (activated)adj(receptor)	62
☐	L30	424/130.1, 135.1, 141.1, 143.1.ccls.	10122
☐	L29	L26 and Flk-1	0
☐	L28	L26 and Flk1	0
☐	L27	L26 and KDR	3
☐	L26	L25 and (phosphorylated)adj(tyrosine)	65
☐	L25	L24 and tyrosine	1402
☐	L24	530/387.3, 388.1, 388.22.ccls.	5136
☐	L23	L20 and YDNT	0
☐	L22	L20 and CDPKFHYDNTAGIS	0
☐	L21	L20 and KDR	36
☐	L20	(phospho)adj(tyrosine)adj(antibod?)	98
☐	L19	(cartlidge)adj(sue)adj(ann)	2
☐	L17	(Y1214)	2
☐	L16	L14 and Y1214	0
☐	L15	L14 and Y1212	0
☐	L14	L13 and (tyrosine)adj(residue)	375
☐	L13	L10 and Flk-1	669
☐	L12	L11 and Y1214	0
☐	L11	L10 and KDR	957
☐	L10	L9 and phosphotyrosine	6014
☐	L9	antibod?	211483
☐	L8	L7 and probe	22
☐	L7	(tyrosine)adj(phosphorylation)same(Flk-1)	101
☐	L6	L5 and Y1214	1

☐	L5	L4 and (tyrosine)adj(phosphorylation)	86
☐	L4	(KDR)same(antibod?)	557
☐	L3	L2 and (KDR)same(Flk-1)same(VEGFR2)	6
☐	L2	L1 and probe	4549
☐	L1	(tyrosine)adj(phosphorylation)	6332

END OF SEARCH HISTORY